**Reconsidering 'vulnerability' in research ethics: A critical analysis and proposal for the refinement of this concept**

Dearbhail Bracken-Roche, BSc

Division of Experimental Medicine, Biomedical Ethics Unit

McGill University, Montréal

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science.

© Dearbhail Bracken-Roche 2016

## Acknowledgements

**Table of contents**

**A note on pronouns**

The pronoun "I" is used to describe research undertaken by Dearbhail Bracken-Roche. The plural pronouns "we" and "our" are used when referring to research undertaken by Dearbhail Bracken-Roche and co-authors. Further details on individual contributions are provided in "*Contributions of authors*", page 12.

## A note on terminology

Use of the term human/research "subject" is debated within research ethics (see e.g., [1] for an overview of this debate). Contemporary research ethics favours use of the term human/research "participant" in order to reflect a fundamental commitment of ethical research: that persons should choose to participate willingly and knowingly in research (i.e., as opposed to being 'subjected' to it). Within this thesis, both of these terms are employed in order to reflect uses within research ethics governance. Some guidelines and policies use the term "subject", while others prefer "participant" – for precision's sake we reflect the language of the policy or guideline in question. This term is also used in reference to historical research events where persons involved were not genuinely informed or voluntarily participating in research.

**Abstract**

In the context of human subjects research, it is widely accepted that some persons are more vulnerable than others and that there exists a moral obligation to pay special attention to and provide additional protections for them. Since the seminal Belmont Report of 1979, research ethics policies and guidelines have employed the concept of vulnerability to alert researchers and research ethics boards (REBs) to this obligation and to guide the assessment and remediation of vulnerability. However, concerns have been raised that current conceptions of vulnerability may be stigmatizing and provide inadequate guidance. Consequently, there exists significant debate about the central components of the concept of vulnerability including its definition, its normative justifications, and the means of its application in research.

The work presented in this thesis critically investigates the conceptual foundations and operationalization of the concept of vulnerability in research ethics, within both research ethics policies and guidelines and the academic literature. Analysis of both bodies of literature was guided by the central components of vulnerability we identified, including the definition, normative foundations, and application of vulnerability.

Manuscript 1 reports on an in-depth analysis of major national and international research ethics guidelines and policies regarding the definition, justification, application, and implications of vulnerability. While the concept of vulnerability is employed within each policy and guideline considered, we found that it is rarely explicitly defined, and is discussed most frequently in terms of vulnerable groups and the implications of vulnerability for researchers and REBs. However, the policies and guidelines were richer than suggested by critiques in the literature. They identify important individual and situational sources of vulnerability and provide a range of options for addressing vulnerability in research. Nonetheless, a significant effort of analysis was required to pool and structure these insights on participant vulnerability. Ultimately, we argue that policymakers in research ethics must focus on explicitly addressing the concerns vulnerability is intended to capture and generating evidence about the outcomes of guidance on vulnerability.

Manuscript 2 reports the results of a critical interpretive review of the concept of vulnerability in the academic literature. Building on the structure refined in Manuscript 1, we examined the insights provided by these accounts on the definition and normative justification of vulnerability, as well as the means through which vulnerability ought to be assessed and addressed. We found that, while accounts of vulnerability in the academic literature provide

important insights, each lacks attention to one or more of the central components of vulnerability. As such, we propose an integrative and functional account of vulnerability enriched by these insights and show how it can be used to provide targeted guidance for researchers, REBs, and others charged with the protection of vulnerable research participants.

Overall, the research reported in this thesis advances our understanding of a central but underexplored concept in research ethics. It highlights gaps within the policies and guidelines and in the academic literature and proposes an integrative and functional account of vulnerability that explicitly addresses them. However, this work also underscores a broader need for evidence-based research ethics. Scholarly reflection can only take us so far, and future work on the concept of vulnerability must focus on gathering evidence about the outcomes and impacts of research ethics guidance and stakeholder perspectives on vulnerability.

**Résumé**

Dans le contexte d'études sur les êtres humains, certaines personnes s'avèrent plus vulnérables que d'autres et il existe une obligation morale de leur offrir des protections supplémentaires. Depuis le Rapport Belmont de 1979, les politiques en éthique de la recherche se sont appuyées sur le concept de vulnérabilité pour sensibiliser les comités d'éthique de la recherche (CÉR) à cette obligation et pour guider l'évaluation de la vulnérabilité. Toutefois, certains affirment que la conception actuelle de la vulnérabilité est stigmatisante et n'offre aucune directive claire. Un débat a lieu autour des composantes centrales de la vulnérabilité, y compris sa définition, ses justifications normatives et les moyens de l'appliquer en recherche.

Ce mémoire examine les fondements conceptuels et l'utilisation de la notion de vulnérabilité en éthique de la recherche, à l'intérieur des politiques et de la littérature académique. L'analyse de ces deux corpus de littérature a été orientée par les composantes centrales de la vulnérabilité que nous avons identifiées, soient sa définition, ses fondations normatives et son application.

Le premier manuscrit présente une analyse détaillée des lignes directrices nationales et internationales en éthique de la recherche ainsi que des politiques en considérant les points suivants: les définitions, justifications, applications et implications de la vulnérabilité. Même si la notion de vulnérabilité est employée au sein de chaque politique considérée, nous avons constaté que ce concept y est très rarement défini explicitement. Il fait plutôt l'objet de

discussions touchant les groupes vulnérables et les implications de la vulnérabilité pour les chercheurs et les CÉR. Cependant, les politiques sont plus riches que ce qu'affirment les critiques dans la littérature. Elles identifient d'importantes sources individuelles et situationnelles de vulnérabilité et suggèrent plusieurs façons d'aborder la vulnérabilité en recherche. Néanmoins, un effort significatif d'analyse a été nécessaire pour rassembler et organiser ces perspectives sur la vulnérabilité des participants à la recherche. Ultimement, nous défendons l'idée selon laquelle les décideurs en éthique de la recherche devraient traiter explicitement des préoccupations saisies par le concept de vulnérabilité et générer des données probantes au sujet des retombées de directives sur la vulnérabilité afin de raffiner ce concept.

Le deuxième manuscrit présente les résultats d'une revue de littérature critique et interprétative portant sur le concept de vulnérabilité dans la littérature académique. En s'appuyant sur la structure raffinée dans le premier manuscrit, nous avons examiné les perspectives fournies par ces conceptions au sujet de la définition et la justification normative de la vulnérabilité, ainsi que les moyens par lesquels la vulnérabilité devrait être évaluée et abordée. Nous avons constaté que les conceptions de la vulnérabilité dans la littérature n'accordent pas suffisamment d'attention à au moins l'une des composantes centrales de la vulnérabilité, même si elles offrent des renseignements pertinents. Nous proposons donc une conception intégrative et fonctionnelle de la vulnérabilité enrichie par ces perspectives et démontrons comment elle peut être utilisée pour guider les agents ayant le mandat de protéger les participants vulnérables en recherche.

En somme, ce mémoire met de l'avant une nouvelle compréhension d'un concept central, mais inexploré, en éthique de la recherche. Il souligne des lacunes existantes dans les politiques et dans la littérature académique et propose une conception de la vulnérabilité qui les aborde explicitement. Toutefois, ce mémoire note un besoin marqué pour une éthique de la recherche basée sur des données probantes. Les travaux futurs sur la vulnérabilité devront évaluer les résultats et les impacts des politiques en éthique de la recherche ainsi que les perspectives des parties prenantes sur la vulnérabilité.

# Contributions of authors

**Manuscript 1:** *The concept of 'vulnerability' in research ethics: An in-depth analysis of policies and guidelines*

Authors: Dearbhail Bracken-Roche, Emily Bell, Mary Ellen Macdonald and Eric Racine

EB and ER developed the idea of conducting a review of research ethics policies and guidelines. DBR developed the search strategy and inclusion and exclusion criteria and gathered the sample with input from EB and ER. DBR developed the coding strategy and conducted the data analysis and EB and ER reviewed. DBR drafted the manuscript and ER served as the primary reviewer and editor, with EB and MEM providing general feedback. DBR drafted the final version of the manuscript and ALL authors agreed on the final version. ALL agreed to inclusion of this manuscript in this thesis. Funding for this study was provided by a CIHR grant held by EB, ER and MEM, an FRQ-S career award held by ER, and graduate scholarships from the IRCM and McGill University held by DBR.

**Manuscript 2:** *Enriching the concept of vulnerability in research ethics: An integrative and functional account*

Authors: Dearbhail Bracken-Roche and Eric Racine

DBR and ER developed the idea for this manuscript. DBR led the literature review and critical analysis with input and review from ER. Both authors contributed to the refinement of the integrative account of vulnerability. DBR led the drafting of this manuscript and ER reviewed it. DBR made final changes to the document and both authors agreed on the final version. ER agreed to inclusion of this manuscript in this thesis. Funding for this study was provided by a CIHR grant held by EB, ER, and MEM, an FRQ-S career award held by ER, and by a graduate scholarship from McGill University held by DBR.

# List of tables

**Chapter 1: Introduction**

…as soon as animate, feeling beings become the subjects of experiment, as they do in the life sciences and especially medical research, this innocence of the search for knowledge is lost and questions of conscience arise.

(Jonas, 1969, p. 219)

Research involving human participants serves to assess the safety of new medicines and innovative therapies and to determine the effectiveness of interventions in education, public health, and other fields. Without human volunteers, key contributions of research to human health and society would never have been possible. However, human subjects research involves complex ethical challenges that require careful reflection and practical solutions [2]. The research context can disempower subjects, putting them in positions of dependency on researchers to both treat them with respect and avoid putting them at unnecessary and unjustified risk of harm [3-7]. The fact that society has recognized a need for research ethics and research oversight suggests that all participants are, in some way and to some degree, vulnerable to harm or wrong (e.g., to physical harm, to the wrong of exploitative treatment, to having their privacy or confidentiality breached) [8]; this is accounted for by the baseline protections (e.g., standards for levels of acceptable risk, appropriate distributions of risks and benefits, or security of personal data) applied to all research participants. However, it is widely assumed within research ethics that some participants are especially vulnerable in ways that demand special consideration and protection (i.e., beyond that applied to all participants). As such, the concept of vulnerability is increasingly referred to in the policies and guidelines that govern research ethics to capture this assumption and guide researchers, research ethics boards (REBs), and other stakeholders in their responses to vulnerability.

Despite its central role, the concept of vulnerability has been heavily critiqued and is widely debated within the academic literature. It has been described as 'vague' and 'under-theorized' [8, 9], and there are debates about the best way to conceptualize the concept in research ethics. This thesis explores the conceptualization and operationalization of vulnerability in research ethics. This is achieved through an in-depth analysis of national and international research ethics policies and guidelines on vulnerability, as well as proposal for an enriched account of vulnerability based on a critical review of the scholarly literature.

In Chapter 2, *Literature review*, the history, critiques of, and major debates surrounding the concept of vulnerability in research ethics are reviewed. The concept of vulnerability first

appeared in the Belmont Report in 1979, and since then it has served in research ethics to designate participants in need of special protection and consideration [8, 10, 11]. The concept of vulnerability has been described as too vague, too narrow, and too broad, and there is a lack of agreement over its definition, normative justifications, and appropriate application.

Chapter 3, *Methodology*, addresses the pragmatist epistemological assumptions in which this thesis is grounded, and outlines our research goals. This thesis includes two manuscripts intended for publication, so this chapter includes methodological details to supplement those provided within each manuscript. Manuscript 1 critically examines the conceptualization and operationalization of vulnerability in research ethics guidelines using the methods of qualitative content analysis. Manuscript 2 is a conceptual exploration of vulnerability within the academic literature, guided by the method of critical interpretive review. The choice of methodology for each manuscript is discussed in this chapter.

In Chapter 4, *Exploring vulnerability in international research ethics policies and guidelines*, Manuscript 1 is presented. This manuscript, entitled "*The concept of 'vulnerability' in research ethics: An in-depth analysis of policies and guidelines*", presents the result of a qualitative content analysis of a sample of national and international research ethics policies and guidelines. We found that, on the whole, this body of literature yielded a richer perspective on the concept of vulnerability than sometimes suggested within the academic literature. However, there are major conceptual gaps within individual policies and guidelines that require the consideration of those charged with their development. This lack of clarity could diminish the usability of the guidance and, as such, undermine its positive impact on research ethics practices.

In Chapter 5, *Exploring and enriching the concept of vulnerability in the scholarly literature*, Manuscript 2 is presented. This manuscript, entitled "*Enriching the concept of vulnerability in research ethics: An integrative and functional account*", presents the outcome of a critical interpretive review of the academic literature on vulnerability in research ethics. We found that key insights regarding the definition, justification, application, and implications of vulnerability are provided in this literature, but no existing accounts integrate these key components in a practically applicable way. As such, we propose an integrative (i.e., integrating these four components) and functional (i.e., practically applicable) account of vulnerability enriched by the existing literature. Further, we illustrate how it can be used to identify situations of vulnerability within the research context and develop targeted responses.

Finally, Chapter 6, *Discussion and conclusion*, addresses two broader themes emerging from this research. The first explores evidence-based, stakeholder-engaged approaches to research ethics and how these would facilitate the refinement of the concept of vulnerability. The second describes a pragmatist approach to research ethics review and explores how adopting such an approach could support a more balanced approach to vulnerability and participant protection. Limitations of the research presented in this thesis are also addressed in this chapter.

**Chapter 2: Literature review**

The term 'vulnerability' is related to the Latin verb *vulnerare*, or wounding, and the noun *vulnus,* or wound [10, 12]. Dictionary definitions of the term 'vulnerable' distinguish three major uses: (1) susceptible to receiving injuries, (2) open to attack or damage, and (3) capable of being physically or emotionally wounded [10]. The language of vulnerability is employed across a wide range of fields [10, 12, 13] for different purposes, but each relates to these central definitional components. For example, in environmental health vulnerability refers to "the degree to which a population, individual or organization is unable to anticipate, cope with, resists and recover from the impacts of disasters" [14]. In economics, 'external vulnerability' describes a country's capacity to maintain financial reserves to pay its external debt [12]. In the military context, vulnerability is "the characteristic of a system that causes it to suffer a… loss of reduction of capability to perform its designated mission" as a result of exposure to certain effects in a hostile environment [15, p.11]. There are, of course, differences in the way this concept is applied across fields but these variations "revolve around an etymological core that correlates vulnerability with conditions of exposure or susceptibility to wounding" [12, p.198] and also relate to notions of adaptability or coping ability [10]. In general then, vulnerability can be thought of as a function of sensitivity, exposure, and coping ability [10].

Vulnerability is also an important and widely-adopted concept in bioethics [13, 16, 17]. While in other fields it may serve predominantly as a descriptive or technical term, vulnerability takes on a normative connotation in bioethics [10, 18]. In other words, vulnerability in bioethics is intended to evoke a response and is underpinned by the idea that "[i]f we can reasonably and reliably prevent [vulnerable persons] being damaged or hurt we should take action" [10, p. 14]. The principles of clinical ethics are underpinned by the vulnerability of persons in need of care and public health ethics is increasingly guided by a concern for addressing the health inequities experienced by vulnerable populations [8, 19]. In both cases, the identification of vulnerability is thought to generate duties for others (e.g., clinicians, public health institutions) and to guide ethical action [10].

The concept of vulnerability has received the most attention in the area of research ethics, and it is in this context that the concept of vulnerability was first introduced to bioethics with the publication of the Belmont Report in 1979 [8, 10-12]. As history has shown, the research context can disempower human participants, putting them in positions of dependency on researchers to treat them with respect and avoid putting them at unnecessary and unjustified risk of harm [20,

21]. As such, research ethics guidelines and practices focus on protecting participants from these risks, through processes of informed consent, requirements regarding the appropriate balance of risks and benefits, and mandated independent review and oversight of human subjects research by REBs [18, 22]. However, some participants are thought to be at increased or special risk of harm or wrong and in need of additional protection [18]; indeed, the history of fraud and misconduct in medical research I will review below has disproportionately impacted socially marginalized or disadvantaged, or vulnerable, groups [23]. This is allegedly the role of the concept of 'vulnerability' in research ethics: it signals mindfulness to this situation [3] and marks a claim to special consideration and protection for these research participants [8, 10, 18].

Despite this important role, the concept of vulnerability has been described as vague and under-theorized in research ethics [8, 9]. While intended as a normative concept, we lack a clear account of how vulnerability generates duties to protect vulnerable participants [8, 18, 22]. Further, there is disagreement about what, exactly, vulnerability is and which strategies should be employed to identify vulnerable participants [8, 11, 18, 24]. The lack of conceptual clarity surrounding the concept of vulnerability leads to confusion about who is vulnerable and what responses are appropriate to address vulnerability, creating a situation in which some research participants may not be adequately protected or other are over-burdened by protections they do not need [3, 4, 25, 26]. Refining the concept of vulnerability would facilitate the development of clearer guidance for researchers and REBs and, ultimately, improved protections for research participants [6].

In order to address the issues associated with vulnerability in research ethics, this thesis critically examine and assesses the conceptualization and operationalization of vulnerability in the policies and guidelines that govern ethical research (Manuscript 1). Further, it critically reviews refined accounts of vulnerability proposed within the academic literature and puts forward an account informed by the work of other authors (Manuscript 2). In order to contextualize this work, this literature review addresses three key areas: the historical origins of the concept of vulnerability, major criticisms of the concept of vulnerability, and major conceptual debates about vulnerability within the literature.

<u>The emergence of vulnerability in the history of research ethics</u>

The field of research ethics was "born in scandal and reared in protectionism" [27, p.167]. Indeed, the current landscape of research regulation and oversight has developed in response to research scandals and revelations of abuse [21]. More specifically, current research ethics practices in industrialized countries have been shaped largely by political responses to the research ethics scandals of the United States in the 1960s [28, 29]. Emerging within this reactive context, the concept of vulnerability has also been shaped by the emerging events and ideas driving research ethics policy. In this section I provide an overview of the history of research ethics in order to contextualize current research ethics thinking especially as it relates to the concept of vulnerability[1].

The foundations of ethics in clinical practice greatly influenced early approaches to the regulation of research [30, 31] and this period has been referred to as a "golden age of assumed beneficence" [30, p.1742]. Research with human subjects proceeded through the early 20th century without formal ethical regulation or oversight because it was assumed that physicians conducted research with the best interests of their patient-subjects in mind as they did during the course of normal medical care [30, 31]. The events of World War II as revealed during the Nuremberg Trials shattered these assumptions and sparked an 'ethical awakening' within the research and biomedical communities [30]. These trials revealed that German physicians were engaged in experiments that inflicted unnecessary and unjustified pain and harm on concentration camp prisoners who were neither informed of, nor given the opportunity to make decisions about, their involvement in scientific experimentation [21, 30].

The Nuremberg Code was created following the Nuremberg Trials. This code consisted of a set of normative statements about which ethical principles ought to govern the use of human volunteers in medical science [32]. Whereas the prevailing Hippocratic approach emphasized physicians' views on the best interests of the patient, the Nuremberg Code emphasized the importance of respecting the autonomy of patient-subjects, seeking their informed consent to participate, and acknowledging their right to withdraw from research, among other protections [31]. Though the Nuremberg Code does not explicitly employ the language of vulnerability, it

---

[1] Note that this section will only address the emergence of the major research ethics policies that, in my view, have contributed most importantly to the concept of vulnerability as it exists today. For example, the Declaration of Helsinki (first adopted in 1964) will not be discussed in this section because, in its first iterations, it did not discuss the concept of vulnerability. However, the Declaration of Helsinki and other research ethics guidelines and policies will be discussed in detail in Manuscript 1.

served to cement the implicit notion that all persons involved in research are vulnerable and in need of protection to some extent [22, 33].

It is widely agreed that in North America, the Nuremberg Code had little impact on the practices of medical researchers at the time. The ideology, orientation, and actions of the Nazi physicians the Code was responding to were viewed as too alien to be relevant to the local context. The dominant view of the medical research community in the United States was that the Nuremberg Code "was a good code for barbarians but an unnecessary code for ordinary physicians" [32]. When placed in this light, it becomes less surprising but no less regrettable that research abuses continued to occur after the creation of the Nuremberg Code. These abuses frequently involved groups of persons who were marginalized in society and had less access to resources and social power. For example, in the United States (U.S.) government-sponsored Tuskegee Syphilis Study, researchers with the U.S. Public Health Service (USPHS) monitored the progression of syphilis in 400 impoverished, largely illiterate African American men and 200 uninfected individuals who served as the control group [34]. For forty years, researchers did not provide subjects with treatment for the disease nor its sequelae, even though treatment options existed at the initiation and emerged over the course of the study [21, 34, 35]. Subjects had agreed to participate because they were promised treatment for syphilis, falsely promised to them by the research team [34]. Further, the USPHS intervened on a number of occasions to prevent subjects from receiving treatment from other sources [34]. By the time the experiment was halted in 1972 due to public outcry, it was estimated that over 100 men had died directly from advanced syphilitic lesions [34].

In addition to the attention generated by the Tuskegee study, Henry Beecher identified twenty-two published studies which were unethical even by the professional standards and practices of the time [28, 36]. Years later, it is clear that Tuskegee and Beecher's report represented only the tip of the iceberg of unethical research conducted both in the U.S. and elsewhere. Interestingly, the cases often pointed to today in the historical narrative of Canadian research ethics did not come to light until the 1980s [28]. For example, CIA-funded research led by Dr Ewen Cameron at McGill University in the 1950s is often used as an exemplar of unethical research in the Canadian context. Commonly referred to as MKUltra, Cameron's work involved subjecting patients seeking treatment for anxiety, depression, and other mental health problems to experimental procedures intended to change human thought patterns and personality

[37]. Not only were these procedures harmful, leading to death and debilitating long-term effects in many cases, but patients were never given the opportunity to consent to their involvement, nor were they informed that their 'treatment' was, in fact, experimental and not designed or intended to benefit them [37]. Tuskegee, Beecher's revelations, and other research that was ongoing at the time but has come to light only (relatively) recently highlighted the potentially problematic relational asymmetry in research involving human subjects. The relative positioning of researchers and subjects creates a relationship where the subjects' welfare depends on researchers' actions [4, 20]. Researchers can, voluntarily or unwittingly, take advantage of subjects' dependency and relative powerlessness, both of which are impacted by subjects' sociopolitical and economic circumstances [3-5, 20].

The research abuses revealed in the 1960s and 70s in the U.S. led, in great part, to the publication of the Belmont Report in 1979 [38, 39]. The Belmont Report delineates guiding ethical principles for the design and conduct of behavioural and biomedical research [21, 38-40], and identifies respect for persons, beneficence, and justice as these fundamental principles. Referred to as the "birth certificate of vulnerability" [10, p.38], the Belmont Report contains the first known reference to this concept within the bio- and research ethics literature [8, 10, 13]. Like the Nuremberg Code, the Belmont Report rests on the assumption that all research participants are vulnerable and in need of protection to some degree. Within the Belmont Report, protection comes in three main forms, each of which represents a concrete application of the fundamental principles. These include: the inclusion of informed consent (application of respect for persons), that the research has a favourable risk/benefit ratio (application of beneficence), and that subjects are selected and enrolled fairly (application of justice) [38, 40, 41].

Within the Belmont Report, vulnerable subjects are distinguished from other subjects (who are, presumably, non-vulnerable) in reference to each of the three principles [41]. Regarding respect for persons and informed consent, it is suggested that vulnerable subjects may be at special risk of being unduly influenced to participate, and that compensation appropriate for other subjects may be unduly influential for vulnerable subjects [40, 42]. The Report also proposes that the assessment of risks and benefits requires additional scrutiny for vulnerable subjects, and "the appropriateness of involving them [in research] should itself be demonstrated" [40]. Finally, with regard to the principle of justice it is argued that vulnerable groups are at special risk for being involved in research simply because of administrative convenience, rather

than for scientific and ethically justifiable reasons. Specifically, the Belmont Report describes "racial minorities, the economically disadvantaged, the very sick, and the institutionalized" as vulnerable groups, for they are readily available for research, and have a dependent status and "frequently compromised capacity for free consent" [40].

The Belmont Report's foundational discussion of vulnerability has been the source of a few important inferences about the meaning of this concept. First, while vulnerability is discussed in relation to each of the three Belmont principles, it is often interpreted as suggesting that vulnerability stems fundamentally a compromised capacity to provide voluntary informed consent or an increased risk of unjustly bearing the burdens of research [41, 43]. Second, the causes of vulnerability are both individual and environmental, with race or health status and social status and positioning being included as key sources. Finally, the Belmont Report suggests that vulnerability has relevance beyond informed consent. This is because vulnerability necessitates a higher standard of justification for the involvement of vulnerable subjects in research and demands restrictions on the provision of research compensation [10].

While broad in its scope and comprehensive in some ways, what is strikingly missing from the Report's discussion of vulnerable groups is a definition of vulnerability [10, 11, 18]. Further, it entails implicit confusion about the meaning and application of vulnerability in research: on one hand, all subjects are vulnerable and require protection primarily through informed consent; on the other hand, some subjects are especially vulnerable, require additional protections, and are owed greater duties in the face of increased risks of unjust and exploitative involvement in research [8].

Since its first appearance in the Belmont Report, the language of vulnerability and vulnerable populations has received wide uptake within the bioethics and research ethics literature. Other guidelines and policies created to guide researchers, REBs, and other stakeholders in the ethical conduct of human subjects started including guidance on the identification and management of vulnerable subjects [11, 18] post-Belmont. For example, the Council for International Organizations of Medical Sciences (CIOMS) released its proposed guidelines for ethical research in 1982, focused on the context of research in developing countries. Within these guidelines, an entire section was dedicated to vulnerability, focusing on persons assumed to have (or likely to have) compromised capacity to provide voluntary informed consent, ranging from children to pregnant women to members of hierarchically-organized

groups [10]. While a majority of research ethics policies and guidelines now make reference to vulnerability, this uptake did not happen as quickly as it did with the CIOMS guidelines. A prime example of this delayed uptake is represented by the Declaration of Helsinki, another seminal code of research ethics. The Declaration of Helsinki was first adopted by the World Medical Agency in 1964 (before both the Belmont Report and CIOMS guidelines) but did not contain any explicit reference to or discussion of vulnerability until its fifth revision in 2000 [10]. While the discussion of vulnerable populations in the Belmont Report sparked much-needed attention to this topic, the problems of the Belmont Report (e.g., its failure to define vulnerability, its vague references to both universal and particular vulnerability) seem to have been inherited by later policy discussions of vulnerability, as well as within the research ethics literature more broadly.

Critiques of vulnerability in academic literature

While there is widespread agreement within the academic literature that some participants are vulnerable and in need of special protection and attention in research, a growing number of authors critique the manner in which the concept of vulnerability is employed in research ethics guidelines and policies [4, 8, 9, 11, 18, 22, 24, 33, 44]. Identifying vulnerability is a necessary precursor to reducing or eliminating it, and there have been increasing efforts to identify vulnerable research participants by group membership [8]. This has been referred to as the 'labeling' [11] or 'subpopulation' [33] approach to vulnerability, and it has been criticized as both too narrow and too broad [9, 18, 43, 45]. In this section, I review the major academic characterizations and criticisms of research ethics approaches to vulnerability.

*Vulnerability is too narrow*

According to its critics, the 'labeling' approach reduces vulnerability to concerns about participants' capacity to provide informed and voluntary consent to research [3, 46]. These critics contend that the purpose of considering vulnerability in research on this approach is to identify any factors that may render a participant's consent less valid [8], and protection of the vulnerable participant is achieved primarily by improving the procedures of informed consent [3, 25, 47]. When this outcome cannot be achieved, vulnerable participants are excluded from research altogether [3, 8, 25]. The consent-based approach obscures the fact that different persons or groups of persons may suffer different kinds of vulnerability that can interact in

different and complex ways [11]. Indeed, it has been argued that this approach obscures other important moral issues the concept of vulnerability ought to capture [18, 24, 48, 49].

For example, Macklin (2003) argues that vulnerability is a susceptibility to exploitation, and exploitation itself is a wrong that ought to be avoided in research. She argues that some persons may be vulnerable to exploitation in research due to background factors including poverty, powerlessness, or dependence on others, and modifications of the process of informed consent would do little to address these issues [48]. Zion, Gillam, and Loff (2000) similarly argue that vulnerability is openness to exploitation cause by a lack of basic rights and liberties, such as rights to freedom of speech, of choice, and of movement [49]. As these authors highlight, and others have emphasized, potential research participants as well as researchers and research teams themselves inhabit complex contexts entailing power structures and dynamics shaped through gender, age, social status, race, and a host of other factors which may potentially create situations of vulnerability within a given research context, [3, 4, 11, 50-53]. Focusing on consent capacity alone "can divert attention from features of the research environment itself, the institutional environment, or the social and economic context that can put participants in harm's way" [24, p.46].

Both historical cases, such as the Tuskegee syphilis study, and recent ones drive home the message that factors beyond consent capacity that can put participants at increased risk of harm or wrong. Dan Markingson, a young man who experienced acute symptoms of schizophrenia, died in 2004 while enrolled in the Comparison of Atypicals in First-Episode Schizophrenia study (CAFÉ) at the University of Minnesota. This example highlights vulnerability-exacerbating factors that informed consent could not have adequately addressed [6]. For example, given Markingson's psychological state, it is entirely possible that his decisional capacity was, in fact, compromised. However, aspects of the CAFÉ research protocol and environment themselves were ethically troubling: the researchers conducting this trial had financial incentives to enrol and retain participants regardless of symptom development, and the protocol itself allowed for the recruitment of subjects who could have been better served by the standard of care [54, 55]. As Rogers (2014) emphasizes, "[a] focus on informed consent will not provide protections against factors such as dangerous protocols, researchers with conflicts of interest, or dysfunctional institutions, all of which make participants vulnerable by increasing their risk of harm." [8, p.67]

*Vulnerability is too broad*

In addition to being described as too narrow, the concept of vulnerability has been critiqued on the basis that it is too broad [24]. The broadness critique centers on the concern that an overly-inclusive approach has been taken to vulnerability, such that entire populations are labeled as vulnerable [11, 24]. Indeed, reviewing five major international research ethics policies, Hurst (2008) found 37 groups and populations identified as vulnerable between them. Several authors worry that such an expansive application of the concept of vulnerability risks includes so many participants that almost anyone could be considered vulnerable [18]. This could eliminate the need for or entitlement to special protections thought to be reserved for vulnerable participants [9, 24, 56]. Furthermore, there is concern that such broad use of the concept of vulnerability renders it "too nebulous to be meaningful" [24, p.46]. Lists can be long and, in the case of lists of vulnerable groups, it is not clear that groups have been labeled based on the same, or even similar, definitions of vulnerability [18].

Just like the narrow approach to vulnerability, the overly broad application of the concept at the population level misses the nuance of context [24]. This leads to the stereotyping of whole categories of individuals, without distinguishing between those who indeed may have special circumstances or characteristics that demand extra attention, and those who do not [24, 25]. Additionally, this approach can be stigmatizing, as it labels persons and their situation based on presumed features rather than on individual characteristics [4, 25]. Identifying entire groups of people as vulnerable can stereotype them as lacking the capacity to care for their own needs or as incapable of being self-determining, which can in turn be used to justify unwarranted and unjust paternalistic measures [57, 58]. In addition to having a potentially detrimental impact on individuals themselves, this points to a problematic imbalance of research ethics principles: protection based on group attribution may fulfil the principle of non-maleficence, but may inappropriately subordinate autonomy and justice, especially when protection entails exclusion [4, 57].

A major concern stemming from both the narrowness and broadness critiques of vulnerability are the potentially negative outcomes this has on potential participants and the progress of research itself. As the narrowness critique highlights, not capturing and addressing the appropriate sources and types of vulnerability means that those whose research participation

might benefit from additional protections may not have access to them. On the other hand, the broadness critique exposes a risk of false categorization, where those who do not actually possess the features or characteristics of concern are considered vulnerable due to their membership in a vulnerable group [9]. When the inclusion of particular subpopulations in research is thought to be unethical, this may exclude them from access to the potential benefits of research [18, 59-61]. As Rogers and Ballantyne (2009) argue, the negative implications of exclusion are particularly pronounced in an age of evidence-based medicine [62]; a lack of representation in research due to perceived vulnerability means that research results cannot answer questions about the safety and efficacy of treatments for end users from these populations, leading to suboptimal options for clinical care [62].

The issue of exclusion is serious, but it is not clear whether labeling participants as vulnerable in research ethics policies leads to their exclusion from research in the current research landscape. It is well documented that American protectionist policies of the 1970s led to the systematic exclusion of women and minority groups from clinical research into the 1990s [62, 63]. While regulations to promote the inclusion of populations labeled as vulnerable are now in place in the U.S. through the National Institutes of Health (NIH) and have been largely successful [62], evidence still suggests that women, and older women in particular, are underrepresented in certain forms of research, e.g., in studies of heart disease and colorectal and lung cancer trials [64, 65], though it cannot be concluded that this is exclusively the result of policies surrounding vulnerability. Elsewhere, the long lists of vulnerable groups may create confusion for those who are supposed to protect the vulnerable, fostering a protectionist approach [18, 26]. For example, vulnerability has been characterized as a 'trump card' [33], stymieing rather than stimulating discussion about research inclusion within REBs, and serving as a warning against the inclusion of vulnerable groups [33, 66]. Further, some authors have expressed concerns that the designation of groups of subjects as vulnerable may lead to their exclusion since researchers may wish to avoid the extra protections and research ethics hurdles entailed by this designation [60, 67].


Conceptual debates about vulnerability in the academic literature

A growing body of academic literature focuses on refining the concept of vulnerability, proposing different approaches intended to overcome the issues with current conceptions of

vulnerability, as outlined in the previous section. However, there have been contrasting arguments put forward about central conceptual elements of vulnerability, which are linked with its critiques. Based on our analysis, these are: (1) the normative justification of vulnerability, (2) the application of vulnerability, and (3) the definition of vulnerability; in this section I provide an overview of these debates.

*Identifying the normative content of vulnerability*

While there is widespread agreement that vulnerable participants are owed special protections, the literature suggests contrasting ways in which this obligation arises. Some accounts of vulnerability are largely concerned with the fairness of participant recruitment and of the distribution of the benefits and burdens of research [43, 48, 49]. On this view, obligations to vulnerable participants are grounded in the principle of justice and a duty to ensure participants are not exploited in research [48, 49, 68]. Other accounts focus on vulnerability as an impairment of autonomy, implying that vulnerable participants are those who cannot provide informed and voluntary consent, and are thus unable to protect their own interests [18, 33, 43, 51, 69]. Another approach to vulnerability conceives of it as stemming from the relationship between research participant and researcher and the degree to which a participant's wellbeing is dependent upon the actions of the researcher within the specific research context [3, 4, 20, 52]. On this view, obligations to vulnerable participants reside within the context of dependency and the duty of care it generates for the researcher [4, 7, 20].

These approaches are not mutually exclusive, and vulnerability may be relevant for a number of reasons and demand responses in accordingly numerous ways [20, 43, 70]. Further, these different approaches may actually reinforce one another. For example, consent- and fairness-based approaches may be mutually reinforcing: persons who cannot consent may be unfairly targeted for recruitment because of this lack of capacity to consent, while persons who are over-recruited to research may be less able to provide voluntary, informed consent because of this external pressure to participate [43]. However, for both practical and theoretical reasons we must at least be able to identify which principles or values guide the applications of special considerations and protections. Practically speaking, there can be gaps between the ethical concepts intended to guide research and the practices at hand, requiring researchers, REBs, and others to understand, interpret, and apply these concepts to their specific context (i.e., within this

gap) [71]. Without an ethical foundation for these interpretations, it can be difficult to understand the intentions of the authoring parties and apply the concept in an appropriate manner to the situation at hand [71]. From a theoretical perspective, vulnerability must have some normative content in order to generate claims for vulnerable participants and corresponding duties for others (e.g., researchers and REBs) [10, 18, 22].

*Applying the concept of vulnerability*

As demonstrated above, the concept of vulnerability has been described as both too broad and too narrow. There are compelling arguments against the narrow application of vulnerability to groups assumed to face challenges providing informed consent. At the same time, applying vulnerability broadly to all groups renders the concept less meaningful. A number of authors have proposed moving to an application strategy in which specific factors within the research context and participants' personal situations that create possible vulnerabilities are identified [3, 11, 22, 50]. Vulnerability should be applied in such a manner that it is comprehensive enough to capture those in need of additional protections without overburdening participants for whom protection beyond the norm is unnecessary [3]. Further, it must provide researchers and REBs with the information necessary to identify those who are vulnerable, as well as to what they might be vulnerable [18, 70], for only then will they be able to effectively address the concerns encapsulated by this concept.

*Defining vulnerability*

The foundational debate about the concept of vulnerability revolves around its definition, with a number of proposals on offer in the academic literature. Hurst (2008) argues that vulnerability, as it exists in the policies and guidelines, lacks an organizing principle. Integrating a number of proposed definitions from other authors, she suggests that vulnerable persons are best conceived of as those who have "an identifiably increased likelihood of incurring additional or greater wrong" [18, 72]. In alignment with the critiques described earlier in this chapter [e.g., see 24], Hurst notes that both individual and situational factors must be evaluated in defining vulnerability because being overly focused on individual characteristics can obscure features of the research protocol or environment that may harm participants. Luna (2009) argues more explicitly that vulnerability ought to be conceived of as 'relational', in that vulnerabilities can

only be discovered by examining an individual in context, and 'dynamic', since one's vulnerability depends on one's context [11]. Further, Luna and Vandepoel (2013) describe layers of vulnerability which arise from interactions between an individual's characteristics and their environment, and which interact with one another to create an inextricably context-dependent vulnerability [73]. As such, there seems to be a shift in the literature away from defining vulnerability as a fixed characteristic of an individual or group and towards a conception of vulnerability as relational and dynamic [6].

<u>The case for refining the concept of vulnerability in research ethics: Summary and research objectives</u>

The concept of vulnerability has, at least implicitly, played a central role in research ethics thinking since the Nuremberg Code of 1947. At a general level, there is agreement that some participants may be especially vulnerable to harm, abuse, or exploitation. However, as this literature review demonstrates the manner in which vulnerability seems to have been conceptualized and operationalized in research ethics guidelines and policies has been the subject of much criticism in the literature. As scholars have responded to these concerns and put forward refined accounts of vulnerability, debate has arisen over key components of this concept, including its normative foundations, its application, and its definition. Until recently, there has been a lack of attention to the concept of vulnerability, and few authors have focused on clarifying and delineating more precisely the central components of this concept [8, 13]. It has been argued that the dominance of individualism and its attendant notions of autonomy and self-sufficiency vulnerability has caused the relative neglect of the concept of vulnerability in contemporary ethics [74]. As vulnerability seems to necessarily entail dependency, it may serve as an unwelcome reminder of the limits of autonomy and individualism [8].

Another potential explanation for the lack of attention to vulnerability is that its meaning is taken for granted [8]. As discussed earlier in this chapter, the concept of vulnerability is employed across a number of fields with slight variations in its specific function, but these variations ultimately revolve around a core of susceptibility, exposure, and resiliency. As such, it may seem self-evident that vulnerability in bioethics refers to "those who are at increased risk of harms, either because they are in hazardous situations or… have a decreased capacity, for whatever reason, to safeguard their own interests" [8, p.62]. However, appeals to self-evidence are untenable for two interrelated reasons. First, the growing critiques and debates highlight that

there is significant variation across understandings of the concept of vulnerability in research ethics. Further, given that the concept of vulnerability has to be applied by researchers, REBs, and other actors in the research process who may not have expertise in ethics, debate and confusion should be addressed in order to facilitate the practical application of the concept.

While due attention has been brought in recent scholarship to the concept of vulnerability in research ethics, it would benefit from further clarification, specifically with relation to its definition, justification, and application. This thesis aims to bring further structure and clarity to discussions of vulnerability in research ethics through a rigorous review of national and international research ethics policies and guidelines (Manuscript 1, Chapter 4). Further, this thesis aims to push the discussion of vulnerability in research ethics forward by proposing a practically-oriented account of vulnerability enriched by key insights from the scholarly literature on this topic (Manuscript 2, Chapter 5).

**Chapter 3: Methodology**

As demonstrated in Chapter 2, a growing body of scholarly literature brings due attention to the concept of vulnerability in research ethics and highlights the issues with current approaches to vulnerability. However, the meaning and operationalization of vulnerability would benefit from further clarification, especially within research ethics guidelines and policies where the full scope of vulnerability has not yet been examined. The overarching goal of this thesis is to examine and critically assess the conceptual foundations of vulnerability in research ethics, with an explicit eye to its practical application and implications. We achieved this goal by (1) conducting an in-depth analysis of vulnerability within research ethics guidance and policies (Manuscript 1, Chapter 4) and (2) critically reviewing the concept of vulnerability within the scholarly literature to propose an enriched account of the concept (Manuscript 2, Chapter 5). We examined the corpus of international guidance separately from peer-reviewed literature because we expected that, given their divergent aims, these documents would provide different levels of detail and focus on different aspects of the concepts of vulnerability.

In this chapter, I explicitly address the epistemological assumptions underlying the research undertaken for this thesis, as well as the methodology employed in the conduct of this research. Given that the manuscripts presenting this research are intended to stand alone (i.e., as distinct publications), each includes some discussion of rationale and methods, as appropriate for their target journals. The additional methodological details provided in this chapter are intended to supplement those provided within each manuscript (Chapters 3 and 4).

Epistemology

In Western philosophic tradition, ethics is thought to consist of "certain ethical standards, rights, or prescriptions which have universal application and are morally absolute and independent of any particular social circumstance" [75, p.xxiv]. On this foundationalist view, knowledge (in our case ethical concepts and principles) exists as an entity distinct from historical or social events [76]. As such, genuine moral or ethical principles or concepts must rest on a foundation that requires no further justification or interpretation [77].

Due to its commitments to interdisciplinarity, its engagement of a multitude of perspectives, and its focus on practical goals, it has been argued that bioethics, a species of applied philosophy [78], operates within a naturalistic paradigm [79, 80]. In contrast to foundationalism, naturalism rejects the notion that knowledge must be grounded in a priori

methods of inquiry [77], taking instead as its fundamental assumption that knowledge is a natural phenomenon embedded in the world of our experience [79]. From a naturalistic epistemological standpoint, attention must be paid to the social and contextual forces that influence the development of knowledge and to the dynamic relationship between knower and knowledge [79].

Bioethics has been described more specifically as a form of moderate pragmatic naturalism [79-81]. Strong naturalism reduces morality to biology, taking ethical concepts to be natural properties and ethical norms are considered to be natural laws [80]. However, a moderate pragmatic naturalistic stance contextualizes the reductionist approach of strong naturalism; it takes ethical norms as following from the interaction between reason and human action [79, 80]. Further, the meaning and value of ethical concepts are inextricably linked to thinking, action, and experience [82].  On this view, ethical predicates cannot be reduced to natural properties, and must take social context into account [81, 83]. Further, concepts that do not have practical consequences, for example on thinking, behaviour, or practices, are of little meaning in bioethics [84, 85]. Abstract ethical concepts must be translatable to practical knowledge and knowledge should be generated, at least in part, with an interest in influencing and improving human actions and practices [83].

Broadly, pragmatism can be thought of a bottom-up approach to ethics in which "thinking is generated in response to (and is intended to resolve) day-to-day dilemmas" [86, p.25]. In addition to remaining sensitive to context and practical application, pragmatism supports an eclectic approach to the refinement of theory and analysis of ethical problems [86]. That is, it supports drawing on and building from the insights of multiple theoretical approaches, enriching discussions of a single ethical concept or issue, for example, by tapping into the resources of diverse normative theories [86, 87].

Our epistemological grounding in moderate pragmatic naturalism thus informed our choice to examine the concept of vulnerability in research ethics, which has not been well-explored from a bottom-up perspective. Grounded in an understanding that this concept must ultimately be applied and have an impact on thinking and practices in research ethics, our work seeks to bring clarity to the notion of vulnerability and make recommendations for research ethics policies and practices.

Manuscript 1 – Methodology: Qualitative content analysis

We conducted an in-depth, comparative analysis of national and international research ethics guidelines and policies to critically assess the conceptualization and operationalization of vulnerability in this literature. Specifically, we employed a systematic content analysis strategy to identify definitions, justifications, and applications of the concept of vulnerability. Content analysis refers to various forms of textual analysis that involve comparing, contrasting, and categorizing bodies of data in order to answer a research question [77] and is often used within a naturalistic paradigm [88]. Content analysis can be either quantitative or qualitative, and the style of analysis chosen dictates how categories are generated and applied to the data, as well as how the resulting data is analyzed [89]. In its quantitative form, content analysis entails the "systematic, objective … analysis of message characteristics" [90, p.1]. In this approach, categories for analysis are generated from a source other than the dataset, applied automatically to the data, and analyzed solely in a quantitative manner, a process which serves to decontextualize the data [89]. In contrast, qualitative content analysis involves the use of categories that are generated, at least in part, in an inductive manner and applied to the data through close reading [89]. Whereas quantitative analysis aims to make general claims based on a study sample, qualitative inquiry aims to understand a phenomenon in depth and detail [89].

We employed qualitative content analysis for our study of research ethics policies and guidelines since we needed a methodological approach that would allow us to explore in-depth the structure and conceptual foundations of vulnerability within this literature. Qualitative content analysis has been used successfully in empirical bioethics to "examine and challenge bioethical assumptions, inform clinical practice, policy-making or theory" [89, p.41], aims that align well with the goals of this research. Adopting such an approach allowed us to meet the goals of this portion of our research.

A key first step after determining that a qualitative approach is appropriate is to explore existing knowledge about the topic. This has a bearing on both data analysis, as previous work can be used to create a conceptual framework that can be used to guide analysis [89]. Given existing work on the concept of vulnerability in research ethics and our initial identification of our three major areas of conceptual interest (definitions, justifications, applications), we employed a more structured and deductively oriented approach to data analysis, drawing on key questions from this literature to inform our examination of the guidelines and policies. However,

we refined our analysis structure inductively, in order to capture another major area of content on vulnerability in research ethics policies and guidelines: responses to (or implications of) vulnerability. We provide further details of our analytic and sampling strategies for this body of literature in Chapter 4 (Manuscript 1, *The concept of 'vulnerability' in research ethics: An in-depth analysis of policies and guidelines*).

Manuscript 2 – Methodology: Critical interpretive review

Initially, Manuscript 2 was intended to take the form of a systematic review of the ethics literature on vulnerability. However, after conducting our search and reviewing a preliminary sample of literature, we determined that exhaustively reviewing the range of accounts provided in the literature would not align well with our ultimate goal of impacting policies and practices surrounding the notion of vulnerability in research ethics. That is, a simple review of the literature would not have supported the theoretical eclecticism and practical orientation of pragmatic bioethics inquiry. Instead, Manuscript 2 draws on the assumptions of pragmatist inquiry and the methodology of critical interpretive review to (1) capture and assess the key insights about vulnerability in the scholarly literature and (2) propose an enriched account of vulnerability that integrates these key insights.

The critical interpretive review is "a longstanding form of bioethics research that aims to develop new knowledge based on capturing and critiquing the key ideas from existing literature" [91, p.525]. A central outcome of the critical interpretive review is the development or refinement of new or existing concepts or theories [91]. In contrast to a systematic literature review, which attempts to capture all papers on a topic, the critical interpretive review does not. While employing a thoughtful literature search strategy, the critical interpretive review aims to capture the key ideas in the existing literature about the topic or research question at hand [91]. This form of review, in which exhaustiveness is measured in terms of ideas rather than through the number of papers themselves, is particularly relevant in bioethics given the nature and role of ethical arguments and justification. That is, whereas an argument about the effectiveness of a given healthcare intervention, for example, would require engagement will all existing evidence, a normative analysis need not be affected by an additional paper published on the same topic [91]. In the first case, a systematic review would be most appropriate, but in the second a critical interpretive review best serves the research goal. Given our goals of (1) critically assessing novel

or refined accounts of vulnerability proposed in the scholarly literature and (2) drawing on key insights in the literature to develop an account that integrates these, we conducted the work of Manuscript 2 in the form of a critical interpretive review.

We drew on the results of a Medline database search, intended initially for a systematic literature review, to capture relevant literature for this phase of the project (see Table 1 for search details). Of the 83 papers captured by this search, we excluded 70 and closely examined 13 for our critical analysis of the four components of vulnerability. We reviewed the reference lists of these papers for additional relevant references, as well as personal references collected by 3 members of the research team (DBR, EB, ER) on the topic of vulnerability in research ethics; this led to an additional 9 papers included for consideration. Given that seminal works on the concept of vulnerability in research ethics has stemmed from the grey literature (e.g., Kipnis' taxonomy of vulnerability which was originally published in a U.S. government-commissioned report on research ethics) [33], Manuscript 2 explores, the scholarly literature (broadly construed) on vulnerability in research ethics, rather than being limited solely to peer-reviewed literature.

We structured our critical review of included papers through the central components of vulnerability refined through our work in Manuscript 1 (i.e., the definition, ethical justifications, application, and implications of vulnerability). In the course of this review we concluded that no account to date in this literature addresses each component while producing an overall practically-oriented, action-guiding account of vulnerability in research ethics. Inspired by pragmatic eclecticism, we thus propose an integrative and functional (i.e., practically actionable) account of vulnerability in research ethics that draws on and extends the insights of other scholars on the aforementioned components of vulnerability. Further details can be found in Chapter 5, Manuscript 2 (*Enriching the concept of vulnerability in research ethics: An integrative and functional account*).

**Table 1 Database search strategy and exclusions for Manuscript 2 (Chapter 5).**

| Database | Medline |
|---|---|
| **Search expression** | mesh(ethics, research) AND ab((vulnerable OR vulnerability)) AND ti((vulnerable OR vulnerability)) |
| **Date** | April 4 2016 |
| **Filter** | Language restrictions: English |

| Results | 83 (85 before language filter applied) |
|---|---|
| **Reasons for exclusion** | Total excluded: n=70<br>• Examination of issues in research with specific vulnerable population, with no significant analysis of vulnerability itself (n=45)<br>• No significant original analysis of the concept of vulnerability itself (n=15)<br>• Analysis of vulnerability outside the context of human subjects research (n=7)<br>Analysis of ethical issues in research with vulnerable populations (n=3) |

**Chapter 4: Exploring vulnerability in international research ethics policies and guidelines**

**The concept of 'vulnerability' in research ethics: An in-depth analysis of policies and guidelines**

Dearbhail Bracken-Roche, BSc,[a,b] Emily Bell, PhD,[a] Mary Ellen Macdonald, PhD,[c] Eric Racine, PhD[a,b,d]

 a. Neuroethics Research Unit, Institut de recherches cliniques de Montréal, 110 Avenue des Pins Ouest, Montréal, QC, H2W 1R7

 b. Biomedical Ethics Unit, McGill University, 3647 Peel Street, Montréal QC, H3A 1X1

 c. Faculty of Dentistry, Oral Health and Society Research Unit, McGill University, 2001 McGill College, Suite 500, Montréal, QC, H3A 1G1

 d. Département de médecine, Université de Montréal, Pavillon Roger-Gaudry, local S-759 2900, boul. Édouard-Montpetit, Montréal, QC, H3T 1J4

Corresponding Author:
Eric Racine, PhD
Director, Neuroethics Research Unit, IRCM
Institut de recherches cliniques de Montréal (IRCM)
110 avenue des Pins Ouest
Montréal, QC H2W lR7
Tel: (514) 987-5723
Fax: (514) 987-5763
Email: eric.racine@ircm.qc.ca

**Conflicts of Interest:** The author(s) have no potential conflicts of interest to disclose with respect to the research, authorship, and/or publication of this article.

Abstract

       The concept of vulnerability has held a central place in research ethics guidance since its introduction in the U.S. Belmont Report in 1979. It signals mindfulness for researchers and research ethics boards to the possibility that some participants may be at higher risk of harm or wrong. Despite its important intended purpose and widespread use, there is considerable disagreement in the scholarly literature about the meaning and delineation of vulnerability, stemming from a perceived lack of guidance within research ethics standards. The aim of this study was to assess the concept of vulnerability as it is employed in major national and international research ethics guidelines and policies. We conducted an in-depth analysis of eleven (five national and six international) research ethics guidelines and policies, exploring their discussions of the definition, application, normative justification, and implications of vulnerability. Few policies explicitly defined vulnerability, instead relying on implicit assumptions and the delineation of vulnerable groups and sources of vulnerability. On the whole, we found considerable richness in the content on vulnerability across policies, but note that this relies heavily on the structure imposed on the data through our analysis. Our results underscore a need for policy-makers to revisit the guidance on vulnerability in research ethics, and we propose that a process of stakeholder engagement would well-support this effort.

Introduction: The function of vulnerability in research ethics guidance and policy

Human subjects[2] research is thought to be fundamentally ethically 'tricky', requiring ethics standards to guide researchers as well as approval and oversight of their research from independent committees. Society allows researchers to invite individuals to participate in research once certain conditions are met, including a research ethics board's (REB, also known as an IRB and REC) determination that risks and benefits are appropriately balanced, that the proposed strategy for subject recruitment is fair, and that voluntary, informed consent will be sought from each potential subject [92]. The concept of vulnerability, which finds it origins in the U.S. Belmont Report of 1979 [10], plays a central role in research ethics thinking, drawing attention to situations where these conditions may not be met [92]. Since 1979, the number of legal and non-legal research ethics policies and guidelines has increased tremendously and, with them, the use and scope of the concept of vulnerability or vulnerable populations [13, 71]. However, there is much scholarly disagreement over the appropriate meaning and application of this concept in research ethics, and policymakers are charged with the challenge of navigating this contentious landscape in the development and refinement of research guidelines and policies [57]. A growing body of literature critiques and aims to advance the way vulnerability is conceptualized and employed in research ethics, with debate regarding foundational elements of this important ethical concept [8, 11, 18, 22, 25, 48-50].


Major debates surrounding the concept of vulnerability in research ethics

There is widespread agreement that some research participants may be particularly vulnerable and in need of special protections, yet the concept of vulnerability itself has been described as "vague" [9] and there is a lack of consensus in the scholarly literature regarding the concept's central features. Contrasting accounts have been proposed regarding the justification of vulnerability and which ethical principles translate into obligations for the special protection of vulnerable research participants. Some accounts propose a justice-based reason for protection, concerned with the fairness of participant recruitment and of the distribution of research burdens and benefits [24, 43]. Others ground vulnerability in a principle of autonomy or respect for

---

[2] A note on terminology: We use the terms "subject" and "participant" interchangeably throughout this paper. Debate exists over these terms, and "participant" is generally preferred because it reminds us of the active and deliberate role individuals should take in their research participation. We have chosen to use both because they are both used in the literature as well as in our sample (e.g., the Tri-Council Policy Statement uses "participant" while the Common Rule uses subject).

persons, suggesting that persons who cannot provide informed and voluntary consent are susceptible to harm because they are not able to protect their interests [18, 43]. These approaches are not mutually exclusive, but we must at least be able to identify which ethical principles define to whom we owe special consideration. In research, there are often gaps between the rules intended to govern and the practices at hand, requiring those tasked with the implementation of these rules to interpret and apply them in their specific context [71]. An ethical foundation is needed for these interpretations, otherwise it is difficult to understand the intentions of the authoring parties or apply the rule to the situation at hand [71]. In this context, better understanding the justifications of vulnerability becomes a crucial goal of scholarly work in this area.

The application of vulnerability and its scope in research has also been a subject of much debate. In particular, vulnerability has been charged with being both too broad and too narrow. An overly broad concept captures all research participants, creating conceptual confusion over the meaning of 'special protections', while an overly narrow concept may leave some vulnerable participants at risk and without needed protection [9, 18, 22, 24]. Practically, a definition of vulnerability must be comprehensive enough to capture those in need of additional protections without overburdening participants for whom protection beyond the norm is unnecessary. Further, it must provide researchers and research ethics boards with the information necessary to identify those who are vulnerable, as well as what they might be vulnerable to. There are compelling arguments against narrow definitions of vulnerable groups that support the identification of specific factors within the research context and the participants' personal situation that create possible vulnerabilities [11].

The foundational debate about the concept of vulnerability revolves around its definition, with various proposals made for its delineation in the literature. Arguing that vulnerability lacks an organizing principle, Hurst (2008) suggests that vulnerable persons are properly conceived of as those who have "an identifiably increased likelihood of incurring additional or greater wrong" [18, p.195]. This account emphasizes that both individual and situational factors must be evaluated in defining vulnerability because being overly focused on individual characteristics can obscure features of the research protocol or environment that may harm participants. Luna (2009) argues more strongly that vulnerability must be conceived of as 'relational', in that vulnerabilities can only be discovered by examining an individual in context, and 'dynamic',

since one's vulnerability depends on one's context [11]. Luna and Vanderpoel (2013) describe layers of vulnerability which arise from interactions between an individual's characteristics and their environment, and which interact with one another to create an inextricably context-dependent vulnerability [73].

To our knowledge, an in-depth analysis of the concept of vulnerability as it exists in the regulations and guidelines that govern human subjects research has not been conducted. This is an important gap because, at present, the scholarly literature seeks to advance the concept without an understanding of the full scope of the regulatory context. Without a clear understanding of the conceptualization of vulnerability in current research ethics, recommendations for its refinement risk being disconnected from the range of policy options. To explore the diversity of options with respect to the enshrinement and application of the concept of vulnerability in research ethics guidelines, we conducted an in-depth analysis of major national and international research ethics guidelines and policies.

Methods

*Sampling*

Inspired by previous research ethics policy analyses [71, 93], we compiled a sample of internationally- and nationally-adopted research ethics guidelines and policies, focusing on Canada (the authors' own regulatory context) and regions with similar demographic and legal structures to Canada, including Australia, the European Union, the United Kingdom, and the United States [93]. We began our search using a compilation of international human research standards produced by the Office for Human Research Protections of the U.S. Department of Health and Human Services [94]. Additionally, we performed secondary searches of the references of any included guidelines and policies for relevant, non-duplicated documents.

Our primary goal was to build a sample of guidelines and policies that discussed or referenced vulnerability in general health research. As such, we excluded those in which vulnerability was not explicitly discussed (e.g., the Nuremberg code) as well as those focused on specific areas of or issues within research (e.g., pediatric research, genetic research), put forward by professional organizations, or published as working papers, drafts, commentaries, or otherwise less broadly adopted documents. Our final sample included eleven guidelines and policies, five of which are nationally-adopted (i.e., within individual countries) and six of which

are internationally-adopted (i.e., across multiple countries). All documents were downloaded and saved for data extraction. Table 2 provides an overview of our sample and the key characteristics of included policies.

*Inter-policy component analysis*

This stage of analysis consisted of an inter-policy analysis, allowing us to capture and explore patterns in the data across our sample. Given our specific interest in understanding how guidelines and policies employ the concept of vulnerability, each document was word-searched for the term "vulnerab". Using this truncated keyword allowed us to identify all uses of the terms 'vulnerability' or 'vulnerable'. We read the broader sections of text surrounding the key terms to facilitate a contextual understanding of how vulnerability was used.

We employed a content analysis strategy, developing an initial coding guide deductively and refining it inductively. We hypothesized, based on the literature (as described in section 1.1), that research ethics guidance on vulnerability should include at least the following basic content: (1) a definition of vulnerability, (2) a discussion of the sources or circumstances from which vulnerability can arise and/or identification of groups likely to be in those circumstances, (3) an explanation of the ethical justification of the concept to aid in its application. A preliminary coding guide was created to capture these content areas. This preliminary guide was applied to a subset of the sample (n=3). Through this 'piloting' stage, the coding scheme was refined inductively by three authors (DBR, EB, ER) to ensure other major areas of content were captured. This resulted in the addition of a fourth content category, 'implications of vulnerability', which captures responses to vulnerable participants laid out within the guidelines and policies. Definitions and rules for the application of each code were developed to ensure rigor and thoroughness. Throughout the coding process, three authors (DBR, EB, ER) engaged in open discussions in order to account for any biases of the primary coder (DBR) and to ensure the full depth of the data would be represented through this analytic strategy. Once final coding was complete, it was reviewed by other authors (EB, ER, MEM) and consensus was achieved through team discussions. A description of each code can be found in Appendix 4-1.

**Table 2 Key characteristics of guideline and policy sample.**

| Guideline/ Policy | Date | Adopted | Abbreviation | Status | Intended Users | Guiding Ethical Framework/ Principles |
|---|---|---|---|---|---|---|
| Declaration of Helsinki | 2013 | Intl | Declaration of Helsinki | A statement of ethical principles proposing how physicians should act in research. Not legally binding. | Primarily physicians. Others involved in medical research with human subjects are encouraged to adopt its principles. | Articles of the Declaration itself are intended as guiding ethical principles for research. |
| Council for International Organizations of Medical Sciences, *International Ethical Guidelines for Biomedical Research Involving Human Subjects* | 2002 | Intl | CIOMS | A guidance document intended to guide the effective application of the Declaration of Helsinki's ethical principles in research, especially in low-resource countries. Not legally binding. | CIOMS member bodies, which include international and national biomedical organizations (e.g., World Medical Association) | Cites three guiding ethical principles: respect for persons, beneficence, and justice |
| UNESCO Universal Declaration on Bioethics and Human Rights | 2005 | Intl | UNESCO Declaration | A universal framework of principles to guide States in formulating legislation and policies, as well as to guide the actions of individuals, groups, communities, institutions and corporations, public and private. | Addressed to States, but also provides guidance for individuals, groups, communities and corporations, public and private. | Articles of the UNESCO Declaration itself are intended as guiding bioethical principles. |
| Directive of 4 April 2001 N°2001/20/EC | 2001 | EU | Clinical Trials Directive | A legislative act that establishes specific provisions for good clinical practice in clinical trials. EU Member States must meet these provisions though the Directive does not legislate how. | EU Member States. | Not explicitly provided. States that "[t]he accepted basis for the conduct of clinical trials in humans is founded in the protection of human rights and the dignity of the human being… as for instance reflected in the 1996 version of the Helsinki Declaration." |
| Regulation of 16 April 2014 N°536/2014. | 2014 | EU | Clinical Trials Regulation | A binding legislative act applying to all clinical trials conducted in the EU. | EU Member States. | Not explicitly provided. |

| | | | | | | |
|---|---|---|---|---|---|---|
| International Conference on Harmonisation, Good Clinical Practice | 1996 | US, EU, JP, AUS, CA | ICH GCP | An ethical and scientific quality standard for designing, conducting, recording, and reporting human subjects research trials. Serves as a unified standard for CA, the EU, JPN, and US to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. | Targeted at those involved in the generation of clinical trial data intended to be submitted to regulatory authorities, especially in CA, the EU, JPN, and US. Can also be used by other involved in clinical investigations 'that may have an impact of the safety and well-being of human subjects'. | Not explicitly provided. States that "clinical trials should be conducted in according with the ethical principles that have their origin in the Declaration of Helsinki". |
| National Statement on Ethical Conduct in Human Research | 2007 | AUS | National Statement | Must be used to inform the design, ethical review, and conduct of human research funded by or taking place under the auspices of the bodies that have developed the Statement (i.e., National Health and Medical Research Council, Australian Research Council, Australian Vice-Chancellors' Committee). | Researchers, members of ethical review bodies, and those involved in research governance, as well as potential research participants. | Describes four guiding 'values and principles': research merit and integrity, justice, beneficence, and respect. |
| Tri-Council Policy Statement, 2nd edition | 2014 | CA | TCPS2 | To be eligible to receive and administer research funds from the federal research agencies responsible for this policy (i.e., Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council), institutions must agree to comply with it. While not required to do so, other organizations and entities are encouraged to adopt this Policy to guide the ethical aspects of the design, review and conduct of research involving humans. | All those involved in the conduct and review of research funded by the federal research agencies, e.g. institutions, researchers, ethics review boards, etc. | Sets out three 'core principles': respect for persons, concern for welfare, and justice. |
| Research Governance Framework for Health and | 2005 | UK | Research Governance Framework | Sets out a framework of principles, requirements, and standards for the governance of research in health and social care and applies to all research relating to | Intended for all those who design research studies, participate in research, host research | Not explicitly provided. |

| | | | | | | |
|---|---|---|---|---|---|---|
| Social Care, 2nd edition | | | | the responsibilities of the Secretary of State for Health. | in their organisation, fund research proposals or infrastructure, manage research, and undertake research. | |
| The Belmont Report | 1979 | US | Belmont Report | A statement of basic ethical principles and guidelines intended to assist in resolving the ethical problems that surround the conduct of research created by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research for the Department of Health, Education, and Welfare. | Those involved in the review and conduct of research. | Lays out three 'basic ethical principles': respect for persons, beneficence, and justice. |
| Title 45 Code of Federal Regulations, Part 46 | 1991 | US | Common Rule | Serves as a federal policy for human subjects research, and applies to all research conducted or supported by or affiliated with the federal agencies by which is has been adopted. | Those involved in the review and conduct of research associated with the federal agencies by which the Common Rule has been adopted. | Not explicitly provided, but the Regulations were created on the basis of the Belmont Report. |

The results of our comparative data analysis are presented in tables, with direct excerpts from the guidelines and policies provided where possible. Two codes (groups and sources of vulnerability, and implications) included more data than others and thus the text has been condensed (e.g., direct citations are not provided). To ensure the fidelity to the data, one author (DBR) condensed this text and another (ER) reviewed it to ensure accurate representation of the guidelines and policies.

*Intra-policy holistic analysis*

After the inter-policy comparative analysis, we examined the conceptualization and operationalization of vulnerability within each policy. Building on the structure developed in our comparative analysis, we assessed the logical consistency between the 4 content areas of vulnerability. More specifically, we analyzed each policy in isolation to examine (1) which major content areas are lacking, (2) whether the four content areas (definitions, justifications, groups and sources, and implications) are consistent (e.g., in their meaning) with one another, and (3) what overall impression a guideline or policy user might have about the concept of vulnerability within the document.

Results: Inter-policy comparative analysis
*Defining vulnerability*

All policies in our sample reference vulnerability and/or vulnerable subjects, but only three of eleven explicitly define these terms (see Table 3). Of these, the CIOMS and TCPS2 guidelines define vulnerability itself, while the ICH GCP instead provides a definition of vulnerable subjects. These definitions share similar structures, all defining vulnerability or vulnerable subjects and identifying paradigmatic sources (or causes) of vulnerability. The ICH GCP definition focuses on issues of consent, where a lack of voluntariness in a subject's decision to participate establishes their vulnerability. The CIOMS and TCPS2 guidelines employ broader language, both stating that vulnerability arises from a subject's lack of ability to protect their own interests. Both identify sources of vulnerability located within the subject (e.g., a lack of decision-making capacity) and in their environment (e.g., a lack of access to medical care). Only the definition provided by the TCPS2 makes explicit reference to another central ethical concept – that of autonomy. This reference suggests an important link between vulnerability and autonomy, though this connection is not further explained.

The definition provided by the TCPS2 is distinct from the others because it explicitly states that vulnerability is context-dependent, and is experienced "to different degrees and at different times, depending on [an individual's or groups'] circumstances". However, qualifying language employed in other policies implicitly suggests a similar view that vulnerability exists on a spectrum or as a matter of degree (see Table 3). The Declaration of Helsinki, National Statement, and Belmont Report, for example, discuss participants who are "particularly vulnerable" (Declaration of Helsinki), "more-than-usually vulnerable" (National Statement), or "especially vulnerable" (Belmont Report). Unlike the TCPS2, no other guidelines in our sample state explicitly that vulnerability should be thought of as existing on a spectrum, or as a feature that can vary between circumstances

**Table 3 Content regarding definitions of vulnerability and detailing the use of qualifying language.**

| | Policy/ Guideline | Explicit definition of vulnerability or vulnerable subjects | Use of qualifying language* |
|---|---|---|---|
| | | **International** | |
| Intl | Declaration of Helsinki | -- | • Some groups and individuals are "particularly vulnerable" (Principle 19) |
| | CIOMS | ""Vulnerability" refers to a substantial incapacity to protect one's own interests owing to such impediments as lack of capability to give informed consent, lack of alternative means of obtaining medical care or other expensive necessities, or being a junior or subordinate member of a hierarchical group." (p. 18) | • Persons with serious, potentially disabling or life-threatening diseases are "highly vulnerable" (p. 65) <br> • Selection of the "least vulnerable" subjects required for research (p. 18) |
| | UNESCO Declaration | -- | • Certain individuals and groups are of "special vulnerability" (Article 8) |
| EU | Clinical Trials Directive | -- | -- |
| | Clinical Trials Regulation | -- | -- |
| US, EU, JP, AUS, CA | ICH GCP | Glossary defines vulnerable subjects as "[i]ndividuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate." (p.8) | -- |
| | | **National** | |
| AUS | National Statement | -- | • Where "potential participants [in dependent or unequal relationships] are especially vulnerable" special measures may be required (p. 53) |

| | | | |
|---|---|---|---|
| | | | • Neonates in intensive care have a "unique developmental vulnerability" (p. 56) <br> • People with a cognitive impairment, intellectual disability, or mental illness have "distinctive vulnerabilities as research participants" and are "more-than-usually vulnerable to various forms of discomfort or stress" (p. 58) |
| CA | TCPS2 | "Vulnerability – A diminished ability to fully safeguard one's own interests in the context of a specific research project. This may be caused by limited decision-making capacity or limited access to social goods, such as rights, opportunities and power. Individuals or groups may experience vulnerability to different degrees and at different times, depending on their circumstances. See also "Autonomy"." (p. 210) | • Participants, researchers, and research ethics board members may be rendered "more vulnerable" during publicly declared emergencies (p. 90) <br> • "The least organizationally developed communities are the most vulnerable to exploitation." (p. 130) <br> • Participants may be "in highly vulnerable circumstances" because of social or legal stigmatization (p. 141) |
| UK | Research Governance Framework | -- | -- |
| US | Belmont Report | -- | • "Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable" (Part C, 1. Informed Consent) |
| | Common Rule | -- | -- |
| *Qualifying language captures nuances about degrees or types of vulnerability. | | | |

*Ethical justifications for the concept of vulnerability*

Many guidelines and policies (CIOMS, UNESCO Declaration, Declaration of Helsinki, National Statement, TCPS2, Belmont Report) provide explicit ethical argumentation relating to vulnerability and/or vulnerable subjects. There is significant overlap across the sample between the principles from which obligations or considerations relating to vulnerability arise (see Table 4 for an overview). In all cases where guiding ethical principles are provided by a policy or guideline, vulnerability-related concerns are discussed in the application of each principle. The normative status of the concept of vulnerability is inconsistent across policies and guidelines. In certain cases (CIOMS, National Statement, TCPS2, Belmont Report), obligations towards vulnerable research participants arise from the application of other fundamental principles. For example, in the TCPS2, obligations towards those in circumstances of vulnerability are entailed by the policy's core principles of Respect for Persons, Concern for

Welfare, and Justice. In others, concerns or obligations related to vulnerability are themselves characterized as fundamental principles. Specifically, principles 19 and 20 of the Declaration of Helsinki focus on vulnerability, with 19 stating that "[s]ome groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm." Similarly, the UNESCO Declaration promotes "[r]espect for human vulnerability and personal integrity" (Article 8) as a principle in and of itself.

The CIOMS guidelines are a unique case in our sample because they characterize vulnerability as both a principle and as a consideration derived from other principles. In the introduction to the CIOMS guidelines, issues of human rights are described as relating to two principles, one of which is the "protection of dependent or vulnerable persons and populations" (p. 11), while the principle of Respect for Persons is described as entailing "at least two fundamental ethical considerations", including "protection of persons with impaired or diminished autonomy, which requires that those who are dependent or vulnerable be afforded security against harm or abuse" (p. 17).

In the remaining guidelines (ICH GCP, Clinical Trials Directive, Clinical Trials Regulation, Research Governance Framework, Common Rule), vulnerability is not explicitly discussed in relation to any ethical principles, nor is it described as a guiding principle itself. In these cases, concerns relating to vulnerable persons seem to serve the role of consideration for ethics review or ethical research with no explicit ethical status.

**Table 4 Content on the ethical justification of vulnerability and its normative status in each policy or guideline.**

|  | Policy/Guideline | Justification for vulnerability | Normative status of vulnerability |
|---|---|---|---|
| | | **International** | |
| Intl | ICH GCP | -- | Consideration for ethics review |
| | CIOMS | The protection of dependent or vulnerable persons and populations is described itself as a principle. Additionally, concerns relating to vulnerability are grounded in both the principles of Respect for Persons and Justice. | Fundamental principle/ Application of other principles |
| | UNESCO Declaration | Respect for human vulnerability and personal integrity is itself a fundamental principle in this framework. | Fundamental principle |
| | Declaration of Helsinki | Concerns related to vulnerability are themselves principles in this framework. | Fundamental principle |
| EU | Clinical Trials Directive | -- | Consideration for |

| | | | ethics review |
|---|---|---|---|
| | Clinical Trials Regulation | -- | Consideration for ethics review |
| | **National** | | |
| AUS | National Statement | Considerations related to vulnerability are discussed in relation to the principles of principles of respect for persons, research merit and integrity, justice, and beneficence. | Application of other principles |
| CA | TCPS2 | The principles of respect for persons, justice (fairness and equity), and concern for welfare all entail special obligations regarding vulnerability. | Application of other principles |
| UK | Research Governance Framework | -- | Consideration for ethics review |
| US | Belmont Report | The principles of respect for persons, beneficence, and justice all entail special obligations relating to vulnerability. | Application of other principles |
| | Common Rule | -- | Consideration for ethics review |

*Identifying vulnerable groups and individuals*

All guidelines and policies in the sample provide means through which vulnerability can be identified. The majority identify subject groups who are likely to be vulnerable. Vulnerable groups identified in our sample are captured in Table 5, along with the corresponding explanations of why a subject group is considered vulnerable or what they are vulnerable to, when these details are available. Notably, while the Clinical Trials Directive and Clinical Trials Regulation, as well as the Research Governance Framework, all identify vulnerable subject groups, none of these policies provide any supporting explanation. Further, only four policies (CIOMS, National Statement, TCPS2, and the Common Rule) provide any explanations of what certain identified groups are vulnerable *to.*

Across the sample, a great number of groups are identified as vulnerable. Counting only those broad groups identified in our table (i.e., excluding the examples of subgroups discussed in the footnote to Table 5), 32 groups; when these subgroups are included, the total number of groups identified as vulnerable expands to 51. Groups most frequently identified are children, minors, or young people (discussed in seven policies), prisoners (discussed in five policies), as well as persons with mental health issues, patients in emergency settings, and certain ethnocultural, racial, or ethnic minority groups (each discussed in four policies). Concerns for the vulnerability of children center around consent, with both the CIOMS and TCPS2 guidelines positing a vulnerability arising from their limited freedom or capacity to consent and the Common Rule emphasizing children's vulnerability to coercion or undue influence. The National

Statement similarly positions the vulnerability of young people relative to capacity and consent, though it is unclear how this policy conceives of the relationship between these concepts. It outlines various scenarios regarding the vulnerability of young people: in some cases, young people may be able to understand information but their "relative immaturity means they remain vulnerable" (p. 50); in other cases they may be "mature enough to understand and consent [though] not vulnerable through immaturity in ways that warrant additional consent" (p. 50); and in yet other cases, young people may be "mature enough to understand the relevant information and to give consent, although vulnerable because of immaturity in other respects" (p. 50). The "other respects" in which immaturity can render young people vulnerable are not made explicit, leaving the designation of vulnerability open to interpretation in this case. Other policies employ similarly open-ended strategies, the CIOMS guidelines most explicitly by listing vulnerable groups and sources of vulnerability, and adding that "[t]o the extent that these and other classes of people have attributes resembling those of classes identified as vulnerable, the need for special protection of their rights and welfare should be reviewed and applied, where relevant" (p. 65).

There is little overlap between the explanations provided by policies and guidelines for other frequently-identified vulnerable groups, and there was a lack of explanation from at least two of them for prisoners, patients in emergency settings, and ethnocultural and racial minorities. For over half of the groups identified across our sample, an explanation of their vulnerability was unclear or lacking entirely. The Clinical Trials Directive and Clinical Trials Regulation and Research Governance Framework provide no explanation or justification for any of the groups they designate as vulnerable, and while the Common Rule specifies that it is concerned with vulnerability to coercion or undue influence, it leaves "handicapped persons" out of this explanation despite also identifying them as a vulnerable subject group. The CIOMS and ICH GCP guidelines, on the other hand, provide definitions of vulnerable subjects and explanations for some vulnerable groups. However, both of these policies include categories of "other vulnerable groups" and fail to provide any connection between these "other" groups and their overarching definition of vulnerability. As such, it is unclear whether they are designated as vulnerable on some 'other' unstated grounds.

**Table 5 Vulnerable groups identified in our sample, as well as explanations for this designation, where available. The table is grouped by category, and organized by the number of times a group is mentioned in the policies and guidelines. Each policy and guideline has been assigned a number**

**which is used to link to corresponding explanations within the table: (1) Declaration of Helsinki, (2) CIOMS, (3) UNESCO Declaration, (4) Clinical Trials Directive, (5) Clinical Trials Regulation, (6) ICH GCP, (7) National Statement, (8) TCPS2, (9) Research Governance Framework, (10) Belmont Report, (11) Common Rule.**

| Vulnerable Group | Policy/Guideline | Explanation |
|---|---|---|
| **Grouped by social status or situation** | | |
| Prisoners | CIOMS (2) ICH GCP (6) National Statement (7) TCPS2 (8) Common Rule (11) | Vulnerable because:<br>• Historically considered vulnerable and "have, at times, been treated unfairly and inequitably in research, or have been excluded from research opportunities" (8)*<br>• Explanation unclear (2, 6)<br>Vulnerable to:<br>• Coercion or undue influence (11) |
| Certain ethnic, racial minority, or ethnocultural groups | CIOMS (2) ICH GCP (6) TCPS2 (8) Belmont Report (10) | Vulnerable because:<br>• Historically considered vulnerable and "have, at times, been treated unfairly and inequitably in research, or have been excluded from research opportunities" (8)*<br>• May continually be sought as research subjects due to ready availability and administrative convenience; have a dependent status and, frequently, compromised capacity for free consent; are easy to manipulate as a result of their illness or socioeconomic condition (10)**<br>• Explanation unclear (2, 6) |
| Patients in emergency settings, prospective participants for emergency research | CIOMS (2) Clinical Trials Regulation (5) ICH GCP (6) TCPS2 (8) | Vulnerable because:<br>• Their incapacity to make decisions creates vulnerable circumstances (8)<br>• No explanation (5)<br>• Explanation unclear (2, 6) |
| Subordinate members of hierarchies or relationships*** | CIOMS (2) ICH GCP (6) National Statement (7) | Vulnerable because:<br>• Voluntary consent may be compromised by expectations of benefit or repercussions from superiors (2, 6)<br>• Pre-existing relationships may compromise the voluntariness of consent because they typically involve unequal status, where one party has influence or authority over the other (7)<br>Vulnerable to:<br>• Being over-researched (2, 7) |
| Economically disadvantaged persons | Belmont Report (10) Common Rule (11) | Vulnerable because:<br>• Dependent status, impaired capacity to consent, easy to manipulate as a result of their illness (10)<br>Vulnerable to:<br>• Coercion or undue influence (11) |
| Homeless persons | CIOMS (2) | • Explanation unclear (2, 6) |

| | ICH GCP (6) | |
|---|---|---|
| Institutionalized persons | TCPS2 (8)<br>Belmont Report (10) | Vulnerable because:<br>• Historically considered vulnerable and "have, at times, been treated unfairly and inequitably in research, or have been excluded from research opportunities" (8)*<br>• Their ability to fully safeguard their own interests in research may be limited, and their situation may compromise the voluntariness of consent in other ways (8)<br>• May continually be sought as research subjects due to ready availability and administrative convenience; have a dependent status and, frequently, compromised capacity for free consent; are easy to manipulate as a result of their illness or socioeconomic condition (10)** |
| Nomads | CIOMS (2)<br>ICH GCP (6) | • Explanation unclear (2, 6) |
| Persons in nursing homes | CIOMS (2)<br>ICH GCP (6) | • Explanation unclear (2, 6) |
| Persons lacking political or social power | CIOMS (2) | • Explanation unclear (2) |
| Refugees or displaced persons | CIOMS (2)<br>ICH GCP (6) | • Explanation unclear (2, 6) |
| Women | CIOMS (2)<br>TCPS2 (8) | Vulnerable to:<br>• In some parts of the world, they may be vulnerable to neglect or harm in research "because of their social conditioning to submit to authority, to ask no questions, and to tolerate pain and suffering" (2)<br>Vulnerable because:<br>• Historically considered vulnerable and "have, at times, been treated unfairly and inequitably in research, or have been excluded from research opportunities" (8)* |
| Countries or communities with limited resources | CIOMS (2) | Vulnerable to:<br>• Exploitation by sponsors and investigators who are relatively wealthy (2) |
| Educationally disadvantaged persons | Common Rule (11) | Vulnerable to:<br>• Coercion or undue influence (11) |
| Members of communities unfamiliar with modern medical concepts | CIOMS (2) | • Explanation unclear (2) |
| Neonates in intensive care | National Statement (7) | Vulnerable because:<br>• Developmental vulnerability (potential for long-range impacts on health and development) (7) |
| Patients in terminal care | National Statement (7) | Vulnerable to:<br>• Unrealistic expectations of benefit (7) |

| | | |
|---|---|---|
| Participants and researchers in research that uncovers illegal activities | National Statement (7) | Vulnerable because:<br>• Vulnerability may arise because of discovery of participants' illegal activity (7) |
| Those with diminished capacity for self-determination | TCPS2 (8) | • Historically vulnerable and "have, at times, been treated unfairly and inequitably in research, or have been excluded from research opportunities" (8)* |
| The least organizationally developed communities | TCPS2 (8) | Vulnerable to:<br>• Exploitation (8) |
| **Grouped by patient/participant condition** | | |
| Children, minors, or young people | CIOMS (2)<br>Clinical Trials Directive (4)<br>Clinical Trials Regulation (5)<br>National Statement (7)<br>TCPS2 (8)<br>Common Rule (11) | Vulnerable because:<br>• Limited freedom or capacity to consent (2, 8)<br>• Vulnerability arising from developmental stage (8)<br>• No explanation (4, 5)<br>• Explanation unclear (7)<br>Vulnerable to:<br>• Coercion or undue influence (11) |
| Persons with mental illness or mental health problems | Clinical Trials Regulation (5)<br>National Statement (7)<br>TCPS2 (8)<br>Research Governance Framework (9) | Vulnerable because:<br>• Historically considered vulnerable and "have, at times, been treated unfairly and inequitably in research, or have been excluded from research opportunities" (8)*<br>• Unclear (5, 9)<br>Vulnerable to:<br>• Various forms of discomfort and stress (7) |
| Elderly persons | CIOMS (2) Clinical Trials Regulation (5)<br>TCPS2 (8) | Vulnerable because:<br>• Likely to acquire "vulnerability-defining traits" (e.g., institutionalization, dementia) (2)<br>• Historically considered a group in vulnerable circumstances "have, at times, been treated unfairly and inequitably in research, or have been excluded from research opportunities" (8)*<br>• No explanation (5) |
| Persons with limited (or no) freedom or capacity to consent | CIOMS (2)<br>Clinical Trials Regulation (5)<br>ICH GCP (6) | Vulnerable because:<br>• Relatively (or absolutely) incapable of protecting their own interests (2)<br>• No explanation (5)<br>• Explanation unclear (6)<br>Vulnerable to:<br>• Exploitation for financial gain by guardians (2) |
| Pregnant or breastfeeding women | Clinical Trials Regulation (5)<br>Common Rule (11) | Vulnerable to:<br>• Coercion or undue influence (11)<br>• No explanation (5) |

| | | |
|---|---|---|
| Adults with learning difficulties | Research Governance Framework (9) | • No explanation (9) |
| Handicapped persons | Common Rule (11) | • No explanation (11) |
| Mentally disabled persons | Common Rule (11) | Vulnerable to:<br>• Coercion or undue influence (11) |
| Persons who have serious, potentially disabling or life-threatening diseases | CIOMS (2) | Vulnerable because:<br>• May be treated with drugs or other therapies with unproven safety and efficacy (2) |
| Very sick persons | Belmont Report (10) | Vulnerable because:<br>• May continually be sought as research subjects due to ready availability and administrative convenience; have a dependent status and, frequently, compromised capacity for free consent; are easy to manipulate as a result of their illness or socioeconomic condition (10)** |
| People suffering from multiple chronic conditions | Clinical Trials Regulation (5) | • No explanation (5) |
| Persons with a cognitive impairment or intellectual disability | National Statement (7) | Vulnerable to:<br>• Various forms of discomfort and stress (7) |
| * It is not clear whether the TCPS2 intends these groups it refers to as having been historically in vulnerable circumstances as still at risk of this. Given that this is mentioned but not negated, we included these groups in our table.<br>** The Belmont Report lists a number of vulnerable groups and a series of explanations of their vulnerability. It is unclear whether certain groups were intended to be linked to certain explanations, so all have been included.<br>***Within this category, specific subject groups are provided as examples. For the CIOMS these are "medical and nursing students, subordinate hospital and laboratory personnel, employees of pharmaceutical companies, and members of the armed forces or police". The ICH GCP adds pharmacy and dental students and persons kept in detention to this list. The National Statement lists "carers and people with chronic conditions or disabilities, including long-term hospital patients, involuntary patients, or people in residential care or supported acumination; health care professionals and their patients or clients; teachers and their students; prison authorities and prisoners; governmental authorities and refugees; employers or supervisors and employees (including members of the Police and Defence forces); service-providers (government or private) and especially vulnerable communities to whom the service is provided". |||

Some policies and guidelines identify sources or circumstances of vulnerability independently, i.e., without any relation or association to a specific vulnerable group. For example, neither the Declaration of Helsinki nor the UNESCO Declaration identifies any particular subject groups as vulnerable. Instead, they identify characteristics of vulnerable participants or key sources of vulnerability (see Table 6). It is important to note that while the TCPS2 does identify certain groups as likely to be in vulnerable circumstances, it qualifies any such labels, emphasizing that "[i]ndividuals should not automatically be considered vulnerable simply because of assumptions made about the vulnerability of the group to which they belong" (p. 54).

**Table 6 Sources of vulnerability identified independently from vulnerable groups.**

| Policy/Guideline | Sources of vulnerability |
|---|---|
| Declaration of Helsinki | An increased likelihood of being wronged or of incurring harm. |
| UNESCO Declaration | Persons may be rendered vulnerable by disease or disability or other personal, societal, or environmental conditions. |
| TCPS2 | Persons may be in vulnerable circumstances because of social or legal stigmatization associated with their activity or identity. |

*Implications of vulnerability in research*

All policies in our sample identify practical implications of vulnerability in research, i.e., responses to vulnerability in the design and review of research and to vulnerable participants themselves. A wide range of implications were identified, some directed explicitly towards REBs and/or investigators but the majority formulated more broadly with no specific group targeted. Further, these implications span the research process, from considerations important in the design of research to actions that must be taken when vulnerable persons are participating in research (see Table 7).

A majority of policies and guidelines identify implications under 'restrictions for research with vulnerable groups or individuals', but these entail both negative and positive duties. Overall, these policies and guidelines propose that the involvement of vulnerable groups in research ought to be restricted to some extent; vulnerable persons they ought to be involved only when the research cannot be carried out with persons who are less vulnerable and special justification is required for this involvement. However, when these persons are involved in research, additional actions are required, such as the design of research that is responsive to their needs or priorities and the provision of benefits relevant to their group/subject population. Across our sample, a common underlying assumption seems to be that vulnerable groups can and should be involved in research, but that additional measures are required to ensure this involvement occurs in an ethical manner. In fact, several policies (CIOMS, Clinical Trials Directive, National Statement, and TCPS2) assert that vulnerable groups have a right to participate in research and access its benefits, and while the others do not identify such an entitlement, none go so far as to state that the outright exclusion of vulnerable groups from research best serves to protect them.

The implications of vulnerability all tend towards careful inclusion rather than outright exclusion of vulnerable groups from research. However, there is more variability regarding the extent to which these protections afford agency to vulnerable subjects. The majority specify considerations and actions for researchers and REBs, with few explicitly identifying the desires of these individuals as relevant in the application of these measures. The TCPS2 in particular puts forth numerous measures intended to promote the agency of those in vulnerable circumstances. For example, it is suggested that they should be afforded opportunities to influence research and that research ought to enhance vulnerable persons' capacity for participation. Furthermore, the TCPS2 guidance states more broadly that vulnerable groups may need or desire special measures to ensure their safety, suggesting a role for participants in the design and implementation of their protections.

In addition to conditions and restrictions for research involvement, the process of informed consent is a major area of focus in the policies and guidelines. Here in particular there is an emphasis on the provision of meaningful support to enable vulnerable persons to offer a fully informed consent to research. Mechanisms of support include ensuring adequate time and an appropriate environment (CIOMS), as well as ensuring that information is fully explained and understood (Research Governance Framework). Additionally, the National Statement uniquely suggested that participants be given the option of using a participant advocate within the consent process.

**Table 7 Implications of vulnerability, grouped by theme.**

| Restrictions for research with vulnerable groups or individuals | Policy/Guideline |
|---|---|
| When research is carried out with vulnerable participants it should be responsive to the needs, conditions, or priorities of the vulnerable group involved | Declaration of Helsinki; CIOMS |
| Vulnerable subjects should be involved in research only when it cannot be carried out with less vulnerable subjects | CIOMS |
| Special justification is required for involving vulnerable groups in research and appropriateness ought to be demonstrated | CIOMS; Belmont Report |
| Children should not be included in early-phase research until therapeutic effects have been shown in adults | CIOMS |
| Opportunities to participate in and influence research affecting their welfare should not be withheld from vulnerable groups | TCPS2 |
| Members of vulnerable groups are entitled to access the benefits of research | CIOMS |
| Children must be involved in studies of medicinal products likely to be of value to them | Clinical Trials Directive |

| | |
|---|---|
| People with a cognitive impairment, intellectual disability, or mental illness are entitled to participate in research, which need not be limited to their particular impairment, disability, or illness | National Statement |
| Research with communities vulnerable to exploitation should strive to enhance capacity for participation | TCPS2 |
| Patients receiving high-risk clinical care should not be inappropriately included in or excluded from research | TCPS2 |
| Risk to vulnerable subjects is justified when it arises from interventions that will provide a direct health benefit, or when it will benefit the subject's population group | CIOMS |
| **Special protections and obligations** | |
| Individuals and groups of special vulnerability should be protected | UNESCO Declaration |
| Special ethical obligations exist towards vulnerable subjects | TCPS2 |
| Vulnerable subjects should receive special/specific protections | Declaration of Helsinki |
| Groups or individuals in vulnerable circumstances may need or desire special measures to ensure their safety in a specific research project | TCPS2 |
| Vulnerable subjects should be afforded security against harm or abuse | CIOMS |
| Special (or additional) protections for the rights and welfare of vulnerable subjects should be applied | CIOMS; Common Rule |
| **Attention and consideration** | |
| Special attention should be paid to trials involving vulnerable subjects | ICH GCP |
| Special attention or regard should be paid to vulnerable communities, groups, or persons | UNESCO Declaration; TCPS2 |
| Researchers and REBs should recognize and address changes in participants' circumstances that may impact their vulnerability | TCPS2 |
| **Research ethics board composition** | |
| REBs reviewing research with vulnerable subjects should include members with expertise on these populations | Common Rule; Clinical Trials Regulation |
| Community members on REBs ought to reflect participant's perspectives, particularly important when participants are vulnerable and/or risks are high | TCPS2 |
| **Assessing harms, risks, and benefits** | |
| For those gauging the severity of harm in research, the vulnerability of a population will be relevant | National Statement |
| The existence of vulnerable circumstances may require greater effort to minimize risks/maximize benefits to participants | TCPS2 |
| Care must be taken to ensure the risks and burdens of proposed research with persons with a cognitive impairment, intellectual disability, or mental illness are justified by potential benefits | National Statement |
| **Recruitment practices** | |
| The vulnerability of persons in unequal, dependent relationships must be taken into account when considering recruiting these persons | National Statement |
| **Process of informed consent** | |
| Consent may need to be re-confirmed in research where participants are vulnerable | National Statement |
| The method of consent in qualitative research depends, in part, on the vulnerability of the research participant; the method must be tailored for their protection | National Statement; TCPS2 |
| When requirements of free, informed, ongoing consent cannot be met, vulnerable participants ought to be involved in decision-making, i.e., obtaining assent, asking about their feelings regarding participation | TCPS2 |
| Clinician-researchers must take care not to overplay the benefits of research participation to vulnerable patients, who may be misled to enter research with false hope | TCPS2 |
| Inducements that may not be excessive or inappropriate for other participants may be undue influences if the subject is especially vulnerable | Belmont Report |
| Care should be taken in the informed consent process to ensure that women vulnerable to coercion have | CIOMS |

| | |
|---|---|
| adequate time and a proper environment in which to take decisions | |
| Care should be taken in the informed consent process for adults with mental health problems or learning difficulties to ensure that information is provided in the appropriate format and that the roles and responsibilities of those involved are clearly explained and understood | Research Governance Framework |
| Additional consent from a parent or guardian may be required for young people who are vulnerable through immaturity in ways that warrant this | National Statement |
| Researchers should invite participants in dependent or unequal relationships to discuss their participation with someone who can support them in making their decision. Especially vulnerable participants in these circumstances should be offered participant advocates. | National Statement |
| **Debriefing** | |
| REBs must assess risks and benefits of debriefing participants and whether debriefing plan is appropriate for participants, especially when they are vulnerable | TCPS2 |

Results: Holistic policy analysis

Of the eleven policies and guidelines in our sample, only two, the CIOMS guidelines and TCPS2, meet our criteria for a full conceptualization of vulnerability, addressing all content areas (see Table 8). In this section, we present the results of our intra-policy analysis of vulnerability with a narrative about each policy statement, addressing (1) which major content areas are lacking, (2) whether the content areas are consistent (i.e., in their meaning) with one another, and (3) what overall impression a guideline or policy user might have about the concept of vulnerability within the document.

**Table 8 Major content areas of vulnerability addressed within each policy or guideline.**

| Policy/ Guideline | Definition: What is vulnerability? | Groups/Sources: Who is vulnerable and why? | Justifications: What ethical concern(s) does vulnerability reflect? | Implications: How should we respond to vulnerability in research? |
|---|---|---|---|---|
| **International** | | | | |
| Declaration of Helsinki | -- | X | X | X |
| CIOMS | X | X | X | X |
| UNESCO Declaration | -- | X | X | X |
| Clinical Trials Directive | -- | X | -- | X |
| Clinical Trials Regulation | -- | X | -- | X |
| ICH GCP | X | X | -- | X |
| **National** | | | | |
| National Statement | -- | X | X | X |
| TCPS2 | X | X | X | X |
| Research Governance Framework | -- | X | -- | X |
| Belmont Report | -- | X | X | X |

| Common Rule | -- | X | -- | X |

*International policies and guidelines*

**Declaration of Helsinki:** The Declaration conveys a harm/wrong-based conceptualization of vulnerability that is internally coherent due to its broad language. It does not identify what these wrongs or harms might consist of and, because concern for vulnerability is presented as a fundamental principle, interpretation cannot be guided by other ethical principles. Implications of vulnerability focus on the need for responsive research, special justification for involving vulnerable persons, and to-group benefits, suggesting these harms include the unfair distribution of the risks and benefits of research.

**CIOMS:** These guidelines present an autonomy-based conceptualization of vulnerability that is comprehensive in scope but lacks internal clarity in its discussion of vulnerable groups. While the provided definition focuses on vulnerability as stemming from an incapacity to protect one's own interests owing to both individual and environmental features, vulnerability is also explicitly linked to justice-based concerns about the distribution of the risks and benefits of research. The identified implications of vulnerability thus correspond to concerns relating to participants' ability to provide free and informed consent and relating to the appropriateness of involving vulnerable participants in research. There is a lack of clarity and consistency, however, in the discussion of vulnerable groups. The CIOMS guidelines distinguishes between 3 types of vulnerable groups: those who are "conventionally considered vulnerable" (pg. 64), those who are vulnerable due to social pressures (i.e., persons in dependent relationship with researchers, such as students or pharmaceutical employees), and "other groups or classes" for whom no explanation is provided and who do not, on their face, bear a significant resemblance to these other groups.

**UNESCO Declaration:** The Declaration is concerned with both a general "human vulnerability" and a more particular "special vulnerability" (Article 8), neither of which are defined. Its identification of personal, societal, and environmental conditions as sources of vulnerability suggests a concept with wide-ranging concerns. The Declaration identifies respecting the personal integrity of vulnerable groups as a key implication, suggesting that vulnerability may consist, at least in part, of risks to one's personal integrity. Since concerns relating to

63

vulnerability are presented as fundamental principles, their interpretation cannot be guided by other ethical principles.

**Clinical Trials Directive:** The Clinical Trials Directive conveys a primarily consent-based vulnerability, with children as the focus of its vulnerability-related regulations. The implications it identifies focus on obtaining proxy consent and assent, but also on the need to avoid financial inducements for participation, suggesting a concern for a risk of exploitation. Other implications include a need to perform research with children in which to-group benefits will be obtained and ensuring the interests of the patient prevail over those of society. As such, in addition to concerns relating to consent, the Directive implicitly relates vulnerability to concerns with the distribution of the benefits and burdens of research. The Directive does not provide an ethics framework, so interpretation of this guidance cannot be guided by ethical principles.

**Clinical Trials Regulation:** The Clinical Trials Regulation conveys a mixed concept of vulnerability, concerned both with issues of consent and increased health risks. While vulnerability is not defined and no explanation for the vulnerability of listed groups is provided, they can be grouped by those assumed to face issues of consent in research (people affected by mental health disorders, minors, and incapacitated subjects) and those who may be at greater physical (i.e., health) risks in research (frail or older people, people suffering from chronic conditions, and pregnant or breastfeeding women). The implications identified do not fall along this consent/health risk distinction, however, with a need for research to improve treatments a key implication for frail or older people, people with chronic conditions, and people affected by mental health disorders, and the need for special expertise in research ethics review identified as a specific consideration for minors, incapacitated subjects, and pregnant or breastfeeding women. No ethical framework is provided in the Regulation to facilitate interpretation of this guidance.

**ICH GCP:** These guidelines present a consent-based concept of vulnerability that lacks internal clarity due to its broad scope of vulnerable groups. Vulnerable subjects are defined as those whose ability to provide voluntary consent may be compromised by social pressures, and the first category of groups listed is clearly linked to this definition. However, it is not clear how the wide range of "other vulnerable groups" relates to this definition or which characteristics are

thought to render them vulnerable. The guidelines do not provide an ethical framework to facilitate interpretation of the concept of vulnerability.

*National policies and guidelines*

**National Statement:** The National Statement suggests a comprehensive conceptualization of vulnerability relating to concerns about consent, fair involvement in research, and a balance of risks and benefits to participants. It favours a group-specific approach to vulnerability, where this concept is discussed largely in reference to specific groups. General statements about vulnerability suggest that it is an important factor when considering the appropriate method of consent. While vulnerability is not defined, explanations for the vulnerability of all identified groups are provided and are discussed with reference to the Statement's guiding ethical principles. Interestingly, explanations of the vulnerability of identified groups the principles from which obligations to those groups stem do not always line up. In some cases, the relationship is clear; the vulnerability of young persons originates in their lack of ability to provide consent and is linked to respect for persons, and the vulnerability of neonates in intensive care originates in the risks of long-term harms and is linked to beneficence. However, while persons in pre-existing/dependent relationships with researchers are said to face issues providing voluntary consent, the key implication relating to this group is grounded in the principle of justice (i.e., ensuring they are not over-researched). Similarly, while persons with terminal illness are said to be vulnerable to unrealistic expectations of benefit (i.e., may have a compromised ability to consent), the key response to this is to balance the benefits and burdens of research and is grounded in beneficence.

**TCPS2:** The TCPS2 presents an autonomy-based conceptualization of vulnerability that is comprehensive in scope. The provided definition of vulnerability states that it stems from a diminished ability to protect one's own interests caused by both individual (e.g., lack of decision-making capacity) and environmental (e.g., lack of access to social goods) factors. Importantly, vulnerability is said to be context-specific and dynamic, discouraging assumptions of vulnerability based on group membership. However, the policy still relies on the identification of groups likely to be vulnerable, as well as the identification of circumstances that can create vulnerability for a participant. While the definition of vulnerability itself is implicitly linked to

the principle of autonomy, obligations towards participants in vulnerable circumstances are more comprehensive and are grounded in the principles of respect for persons, concern for welfare, and justice.

**Research Governance Framework:** The framework conveys a consent-based conceptualization of vulnerability that is narrow in scope, labeling adults who may have issues with understanding and decision-making as vulnerable. Consistent with this, the implications of vulnerability focus on providing participants with the necessary support in the informed consent process. Since no ethical framework or principles are discussed relative to vulnerability, these cannot be used to facilitate interpretation of the guidance.

**Belmont Report:** The Report conveys a consent-based conceptualization of vulnerability that lacks clarity in the features of vulnerability it aims to target. It is assumed that vulnerable subjects have a "dependent status and frequently compromised capacity for free consent", which seems to form the basis of their vulnerability. Special considerations about vulnerable subjects are discussed in reference to respect for persons (ordinary inducements may be come undue influences for vulnerable populations), beneficence (special justification is required for research with vulnerable subjects), and justice (vulnerable subjects must be protected from over-recruitment to research).

**Common Rule:** The Common Rule conveys a consent-based conceptualization of vulnerability that lacks internal clarity regarding its scope. A number of groups are identified as vulnerable, including handicapped persons, but while the other groups are said to be vulnerable to coercion or undue influence, no explanation is provided for handicapped persons. Similarly, the implications of vulnerability include concern for equitable subject selection and the provision of additional safeguards, but handicapped persons are never associated with these protections. Without a definition of vulnerability, it is not clear what special vulnerability handicapped persons may be faced with in research.

Discussion

The objective of this analysis was to describe the concept of vulnerability in research ethics policies and guidelines, and to assess how it is conceptualized and operationalized. All policies employed the concept of vulnerability but very few define it. Instead, vulnerability is most frequently discussed in terms of vulnerable groups, with some attention given to the sources of vulnerability, and the implications of conducting research with vulnerable participants. In many respects the policies come out, on the whole, as richer and more complex than some scholarly analyses of the concept of vulnerability suggest [8, 11, 69]. For example, the policies and guidelines identify sources of vulnerability that are both individual and situational [11, 50]; vulnerability can stem from a lack of capacity or from one's health status, but also from social pressures that may impact one's ability to make a free and informed decision, consistent with some scholarly perspectives [33]. Responding to vulnerability requires caution and special consideration on the part of researchers and REBs but, ultimately, the implications identified in our study suggest that participant vulnerability need not signal a need for exclusion from research. The few explicit definitions in our sample define vulnerability as a deficiency of the participant, as an inability to protect one's interests in research. The majority of other guidelines and policies implicitly convey a similar conceptualization of vulnerability as a deficiency in a participant's ability to provide voluntary informed consent. Accordingly, even though, there is some diversity and richness in policies, it tends to be scattered across multiple policies and relies on implicit assumptions about the definition and nature of vulnerability. Indeed, a significant analytic effort was required to bring structure to the data and yield the guidance captured in this paper. We further discuss how our findings relate to: (1) previous critiques found in the scholarly literature and (2) the role of stakeholder engagement in the process of refining the concept of vulnerability in research ethics policies and guidance.

*Previous critiques from the scholarly literature*

The scholarly literature has voiced several critiques of vulnerability in research ethics guidelines. First, concerns have been raised that the manner in which vulnerability is defined and operationalized in research ethics governance stereotypes and reinforces stigma about whole categories of individuals [4, 24, 25]. Our results reinforce these concerns, as the reliance on listing groups of vulnerable persons is rampant. This labeling [11] or sub-population [33] approach, does little to bring attention to the importance of context and of assessing the

characteristics of individual research participants beyond their membership in a group [11, 18, 21, 25]. It is important to note that research protocols create groups through sampling "regardless of whether the sample is drawn from a naturally occurring community" [25, p.2221]. Understanding this point underscores the fact that group membership in this context may not well capture the various relevant aspects (and potential vulnerabilities) in an individual participant's situation. This may result in inappropriate and ineffective protections being applied in some protocols. Group listings may also cause confusion due to the broadness of some labels (e.g., persons with mental illness or mental health problems). Furthermore, it seems that the designation of some groups as vulnerable may be based on assumptions not supported by evidence (e.g., the designation of pregnant women as vulnerable to coercion or undue influence in the Common Rule).

Another major concern has been that vulnerability as conceived of in the guidelines focuses overwhelming on a lack of ability to consent [3], blinding researchers and REBs to other relevant types of vulnerability, relating, for example, to an increased risk of exploitation [48, 68] or a lack of basic rights [49]. While vulnerability is rarely defined, the majority of policies and guidelines convey implicitly that vulnerability is fundamentally an inability to provide free and informed consent. However, the implications of vulnerability often move beyond consent, addressing issues of fair subject selection and favourable risk benefit assessments. In addition to providing explicit definitions for what, exactly, is meant when the term 'vulnerability' is used, the clarity and usability of policies and guidelines could be improved by ensuring that these definitions clearly relate to the concerns with which vulnerability is associated.

Though they recognize both individual and contextual sources of vulnerability, all policies and guidelines conveyed that vulnerability is a personal characteristic. Even the TCPS2, with its notable emphasis on vulnerability as a context-dependent feature, ultimately defines it as a person's inability to protect their own interests in research. In contrast, a growing body of scholarly literature converges around the notion that vulnerability is a relational feature, borne of power asymmetries between participants and research staff, investigators, and institutions [3, 4, 6]. Adopting such a view in research ethics guidelines may better serve participants, encouraging measures that would empower and promote their agency in the research context [6]. Furthermore, the focus on research participants neglects how research environments (e.g., the existence of conflicts of interest) can actively contribute to disempowering research

participants/research subjects and thus create the need for remediation that does not necessarily concern the research participant per se [3, 11].

*A need for evidence and stakeholder engagement to refine research ethics policies and guidance on vulnerability*

Research ethics guidelines and policies typically stress the importance of vulnerability. However, it has been argued that vulnerability is not a substantive ethical concept in itself, serving only as a marker of other research ethics concerns already captured by existing concepts, such as harm or consent [95]. This is certainly an important conceptual concern, but what may be of greater relevance in the realm of policy development is the degree to which the concept of vulnerability is a useful, effective tool for those designing, reviewing, and conducting research [11, 18, 72]. It may be the case that vulnerability merely serves to signal concerns relating to other pre-existing ethical concepts, but if these concerns would be otherwise missed, the concept would then be proven to have a vital practical function in research ethics. A few authors have made explicit claims to that effect. For example, Kipnis (2003) argues that vulnerability stems from impairments to one's ability to provide voluntary informed consent. He identifies seven types of vulnerability which all signal potential issues with a participant's ability to consent: incapacitational, deferential, and medical vulnerability, which all relate to characteristics of the participant themselves, and juridic, allocational, social, and infrastructural, vulnerability, all of which relate to factors in the participant's environment [51, 69]. These categories help bring attention to more specific aspects that generate vulnerability. Luna (2009) argues that vulnerability, when conceived of as dynamic, flexible, and inessential, can serve as "a fine grain tool to analyze, interpret, and evaluate the research situation" [11, p.130]. She proposes that vulnerability be conceived of through the metaphor of layers, in which different layers of vulnerability can operate and interact within a given participant's circumstances. Luna's account of vulnerability thus provides researchers and REBs with a conceptual tool with which to examine a research participant's circumstances, identify potential vulnerabilities (e.g., relating to capacity or social pressure in the consent process), and develop targeted strategies for their remediation.

In spite of these more sophisticated proposals, there is a dearth of empirical evidence on the functioning of research ethics committees and outcomes of research ethics policies and, to our knowledge, few studies have examined the impact or understandings of the concept of

vulnerability based on research ethics guidelines and/or more elaborate scholarly accounts. Empirical evidence has shown that an understanding of vulnerability in the context of research cannot be assumed to be universal: in a study with Russian and Romanian research ethics trainees, Loue and Loff (2013) found that, at the initiation of their training, their existing understandings of vulnerability varied considerably from conceptualizations in the international guidelines [96]. Another study gathered researchers' perspectives on vulnerability in HIV/AIDS clinical trials and on the Common Rule guidance related to vulnerability [97]. Sengupta et al. (2010) found that researchers assessed vulnerability in relation to situational factors that can render participants vulnerable, and that they emphasized the need to assess vulnerability on a case-by-case basis (i.e., rather than relying on a group-based strategy) [97]. Taken together, these studies underscore the need for guidance and policy-makers to clearly delineate and define the concerns vulnerability is intended to encompass, and to assess the alignment of these views with those of research stakeholders. Further, there is a need to assess the outcomes of vulnerability-related guidance and policy and to understand whether protections are actually effective and their impact on vulnerable participants themselves. For example, there are crucial questions about the actual usability and impact of such guidelines as well as the potential need for mid-level guidance between general guidelines and the actual analyses of REBs [98]. It has been suggested that more elaborate, on-the-ground guidance on vulnerability would be beneficial to help REBs direct their attention to the most pertinent concerns [33]. In the process of developing such guidance, the voices of those concerned by the application of what sometimes appears as a label of vulnerability could be instrumental in moving forward and avoiding the perpetuation of stereotyping or stigmatizing accounts of vulnerability [6]. In this endeavour, the perspectives of researchers and REBs, but also of research participants, who seem to have been largely left out of the development of research ethics guidelines, could be investigated.


Conclusion

Our in-depth analysis of human research ethics guidelines and policies allowed us to analyze different perspectives on the concept of vulnerability, including the definitions, justifications, sources, and implications of vulnerability for researchers and REBs. In some respects the synthetic/interpretive accounts yielded a richer perspective than sometimes admitted in scholarly literature. At the same time, there are conceptual gaps within individual guidelines

and policies that require the attention of those charged with their development. This lack of clarity could diminish the usability of the guidance put forth in policies and therefore undermine its impact on research practices. Policy-makers should revisit the concept of vulnerability to ensure each of its key components are spelled out, and that these "components" are internally consistent (i.e., within individual guidelines). Practically-oriented refinement of vulnerability could be facilitated by engaging research stakeholders) and examining the concrete impact of guidance and policy related to vulnerability.

**Chapter 5: Exploring and enriching the concept of vulnerability in the scholarly literature**

**Enriching the concept of vulnerability in research ethics: An integrative and functional account**

Dearbhail Bracken-Roche, BSc,[a,b] and Eric Racine, PhD[a,b,c]

a. Neuroethics Research Unit, Institut de recherches cliniques de Montréal, 110 Avenue des Pins Ouest, Montréal, QC, H2W 1R7

b. Biomedical Ethics Unit, McGill University, 3647 Peel Street, Montréal QC, H3A 1X1

c. Département de médecine, Université de Montréal, Pavillon Roger-Gaudry, local S-759 2900, boul. Édouard-Montpetit, Montréal, QC, H3T 1J4

Corresponding Author:
Eric Racine, PhD
Director, Neuroethics Research Unit, IRCM
Institut de recherches cliniques de Montréal (IRCM)
110 avenue des Pins Ouest
Montréal, QC H2W lR7
Tel: (514) 987-5723
Fax: (514) 987-5763
Email: eric.racine@ircm.qc.ca

**Conflicts of Interest:** The author(s) have no potential conflicts of interest to disclose with respect to the research, authorship, and/or publication of this article.

Abstract

      The concept of vulnerability is widely used in research ethics to signal attention to participants who require special protections in research. However, this concept is vague and under-theorized, and there is growing concern within the scholarly literature that the dominant approach to vulnerability (as exemplified by research ethics regulations and guidelines) is ethically problematic and, in fact, not very guiding. Agreement is emerging that a shift should be made from categorical (which focus on delineating vulnerable groups) towards analytical (which focus on defining and analyzing the types and sources of vulnerability) approaches to vulnerability. Beyond this agreement, however, scholars have been advancing competing accounts of vulnerability and struggling to reach consensus about the appropriate conceptualization and operationalization of vulnerability in research ethics. We propose that a comprehensive account of vulnerability for research ethics must include a definition and normative justifications, as well as a discussion of the application and implications of vulnerability. Concluding that no existing accounts of vulnerability integrate these components in a functional (i.e., practically applicable) manner, we propose an integrative and functional account of vulnerability in research ethics enriched by the scholarly literature. Drawing on the context of research on the use deep brain stimulation (DBS) in the treatment of treatment-resistant depression (TRD), we illustrate how the integrative-functional account can be used to generate targeted responses to vulnerability in research. Further, we show how this account is both inspired by, and is well-suited to application within, a pragmatist, evidence-based approach to research ethics. While ultimately there are considerable concerns to be addressed within the existing research ethics policies and guidelines on vulnerability, the integrative-functional account can serve as an analytic tool to help researchers, REBs, and other tasked with the protection of research participants fill in the gaps within the current landscape of research ethics governance.

Consider what effects, which might conceivably have practical bearings, we conceive the object of our conception to have. Then, our conception of these effects is the whole of our conception of the object… there is no distinction of meaning so fine as to consist in anything but a possible difference of practice.

– Charles S. Peirce

<u>Introduction</u>

The concept of vulnerability has been widely used in the bioethics literature and has been a topic of particular interest within the area of research ethics [8, 10]. The notion of vulnerability is central to the ethical review, conduct, and oversight of research; all major national and international research ethics guidelines and policies employ the language of vulnerability to draw attention to persons who require special consideration to ensure their research participation proceeds in an ethical manner [18, 57]. There is growing concern within the scholarly literature that the dominant approach to vulnerability (as exemplified by research ethics regulations and guidelines) is ethically problematic and, in fact, not very guiding. Agreement is emerging that research ethics requires a shift away from categorical (which focus on delineating vulnerable groups) towards analytical (which focus on defining and analyzing the types and sources of vulnerability) approaches to vulnerability [16]. Beyond this fundamental agreement, however, scholars have been advancing competing accounts of vulnerability [11, 22, 33, 44, 50, 69, 73] and struggling to reach consensus about the conceptualization and operationalization of vulnerability in research ethics [16, 22, 57, 99]. In the meantime, research staff and REBs are faced with the challenge of assessing and appropriately responding to vulnerability, and their action, or inaction, has concrete implications for potentially vulnerable research participants. Moreover, it is crucial to keep in mind the needs of stakeholders involved in on-the-ground research ethics and to be mindful of the day-to-day reality of research conduct in developing a refined account of vulnerability [100].

In this paper, we will address the much-debated issue of how the concept of vulnerability should be defined and operationalized in research ethics, drawing on key insights from the scholarly literature to address it. Working from a pragmatist approach to bioethical inquiry, we adopt a view of vulnerability as an analytic tool that should allow research stakeholders to identify and address problematic relational dynamics within a research project. Pragmatism also

paves the way to conceptual enrichment through a theoretical eclecticism that allows us to draw on the insights of scholars working from a range of theoretical assumptions [101]. Further, it stresses the importance for the concept of vulnerability to make a practical difference in light of the aims pursued and the problematic situations of exploitation and injustice that this concept was originally intended to capture [40].

Our approach is as follows: first, we identify four major questions about vulnerability that have been answered differently within different accounts. This critical review allows us to identify the four central components that an *integrative* (building from the insights of the literature) and *functional* (one which leads to actionable differences in ethics review and research ethics) account should include. Then, building on and enriching key insights from the peer-reviewed literature, we propose an integrative and functional account of vulnerability in research ethics that facilitates a thorough examination of the sources of vulnerability and identification of the specific concerns in question. The thorough analysis this account entails enables users to develop targeted strategies to respond to these concerns. In the last section of this paper, we briefly sketch out this process, illustrating how the integrative-functional account can shed light on key criteria of ethical research and how it can be applied in the spirit of pragmatism [86] to analyze the vulnerability of participants in the context of a specific research project.

## Recurrent problems with the concept vulnerability

Since its first explicit use in the Belmont Report, discussion of the concept of vulnerability has become widespread, and it is addressed within most major national (e.g., the 'Common Rule' in the U.S. and TCPS2 in Canada) and international (e.g., the International Conference on Harmonization Good Practice Guidelines, or ICH-GCP, and the Declaration of Helsinki) research ethics guidelines. Four major and interwoven areas of debate have surfaced with respect to different accounts of vulnerability, thus plaguing a strong conceptual understanding of the concept as well as its consistent and concrete application.

### *What is vulnerability?*

Most major research ethics guidelines employ the concept of vulnerability but few explicitly define it (see Manuscript 1). An in-depth analysis of vulnerability in international

research ethics guidelines found that of the eleven that employ the concept,[3] only three define it or characterize what it means to be vulnerable (see Manuscript 1). Other guidelines rely instead on listing categories of vulnerable participants, implying that group membership defines vulnerability. This simplistic approach is sometimes described as a paradigm of 'intrinsic' or 'static' vulnerability since it suggests a fundamental link between one's characteristics, such as race, gender, or health status, and one's vulnerability [3, 11]. Relying on lists of vulnerable persons is problematic as it is often not made clear what characteristic or set of characteristics is shared by these groups or what it is about these characteristics that render those who possess them vulnerable.

An important but under-recognized aspect of vulnerability (at least within the policies and guidelines) (see Manuscript 1) is that what the concept describes is tied to why it matters; an ethically-relevant construct will have force if it has some normative foundation or grounding such as an ethical principle or a value. The Council for International Organizations of Medical Sciences (CIOMS) guidelines, for example, define vulnerability as "a substantial incapacity to protect one's own interests" [102]. This definition opens the door to different reasons why vulnerability occurs, as well as why it matters, including concerns about threats to the voluntariness of consent or the fairness of research recruitment and participation itself.

*Why does vulnerability matter?*

Research ethics guidelines implicitly reflect a fairly broad range of normative reasons why vulnerability matters from an ethical standpoint. Originally, the Belmont Report addressed the ethical significance of vulnerability with reference to its three core principles of respect for persons, beneficence, and justice. It characterizes vulnerability as stemming primarily from a lack of capacity to provide free and informed consent with implications for processes of consent (respect for persons), the conditions under which recruiting vulnerable participants is justified (justice), and the assessment of risks and benefits for these populations (beneficence). Similarly, within the academic literature, consent-based, harms-based, and justice-based views have been

---

[3] This study included six internationally- and five nationally-adopted guidelines and policies. International guidelines: Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects, International Council on Harmonization Good Clinical Practice (ICH GCP), Declaration of Helsinki, UNESCO Declaration on Bioethics and Human Rights, and the European Union's Clinical Trials Directive and Clinical Trials Regulation. National guidelines: the National Statement on the Ethical Conduct of Research (Australia), the Tri-Council Policy Statement (TCPS2) (Canada), the Research Governance Framework for Health and Social Care (UK), and the Belmont Report and 'Common Rule' (USA).

identified [18, 43]. Since the Belmont Report's pioneering discussion of vulnerability, the concept has most often been grounded, either implicitly or explicitly, in the principle of autonomy [3, 24], leading to concerns that it is too narrow and does not adequately capture concerns associated with exploitation or increased risk of harm [18, 48].

Confusion about the actual 'foundations' of the normative importance of vulnerability needs to be addressed. A lack of clarity about which principle(s) inspire the concept can lead to confusion about who is vulnerable. For example the recent proposed revisions to the U.S. Common Rule suggest that pregnant women are vulnerable but, paradoxically, express that vulnerability is a compromised ability to provide free and un-coerced consent [103]. A harm-based form of reasoning could ground the inclusion of pregnant women in the discussion of vulnerable populations of this policy, but this commitment is not spelled out and leads to confusion.

*Who is vulnerable and why?*

The paradigm of 'intrinsic' or 'static' vulnerability has been described as too broad, with the category of vulnerable persons expanded to the degree that most potential research participants would fall into some group of vulnerable subjects [24]. Indeed, major international research guidelines collectively capture at least 35 distinct groups/sources of vulnerability[4] (see Manuscript 1). Given that vulnerability is thought to warrant special protections or considerations (i.e., beyond the standard offered to research participants in general), an account of vulnerability that includes all participants eliminates the meaning of and need for special protections [9, 56]. In a context where there is no shared definition of vulnerability, and often no definition in the guidelines intended to govern ethical research, those in a position to decide about or implement protection for vulnerable research participants may not have the information or understanding required to assess which participants really need additional protection and what form this protection ought to take.

Group- or list-based accounts of vulnerability are also problematic because they stereotype whole categories of persons based on single characteristics that surely cannot account

---

[4] We say "at least" 35 distinct groups/sources because the policies and guidelines often include examples within some larger categories and counting each of these would further expand the number of distinct groups. For example, the CIOMS and ICH GCP guidelines identify subordinate members of hierarchies as a vulnerable group and expand this category by identifying further subgroups including medical and nursing students, members of the armed forces or police, governmental authorities and refugees, and so on.

for a wide range of complex situations [24, 42, 60]. This strategy misses the nuance of context and impedes recognition of the fact that, in general, group membership alone is not a reliable indicator that a person possesses the characteristic of interest for vulnerability, and that vulnerability is context-dependent [3, 11, 24]. That is, vulnerability may arise in certain circumstances and not others because of the timing of research, its emotional impacts, one's prior experiences, or other personal factors [3, 11, 22, 24, 69]. Failing to recognize this may mean that safeguards may not be effectively tailored to the vulnerability (or vulnerabilities) of individual participants. Group- or list-based accounts of vulnerability also increase the risk of false categorizations, in which persons who are not truly in need of additional protections in the context of a specific project may be considered so because of group membership, or those who may require these protections are not afforded them because they are not captured by traditional lists of vulnerable groups [9, 11]. Additionally, labelling groups of persons as categorically vulnerable can also reinforce stigma [3, 4, 25].[5]

*What are the implications of vulnerability?*

Arguably the most important reason for discussing vulnerability in research ethics is so that it can be appropriately addressed and responded to by researchers and REBs and other stakeholders in the research enterprise. Concerns have been raised that the paradigmatic approach to vulnerability leads to the exclusion of vulnerable groups from research [4, 60]. Interestingly, the guidance on vulnerability does not suggest that research with participants in vulnerable circumstances is categorically unethical; in fact, it is widely suggested that vulnerability can and should be addressed in order to fulfill an obligation to provide the potential benefits of research to such persons (see Manuscript 1). However, the lack of clarity surrounding

---

[5] The issues associated with identifying who is vulnerable and why draw attention to a broader issue concerning the anticipatory structure of research ethics review. Within the current broadly-accepted structure of research ethics review, researchers, policy-makers, and REBs must pre-assess the potential vulnerabilities of their target population and propose any special protections from this rather distal and mediated position. While researchers may be well-positioned to observe the effects of participant protections (that is, the outcomes of these pre-assessments), it is uncertain whether they act upon this positioning. Further, policy-makers and REBs – those who hold the most power in the regulation of ethical research – do not have the opportunity to judge whether they have accurately assessed situations of vulnerability. As such, these actors cannot modulate their perspectives on the vulnerability of certain populations (or associated with certain characteristics) based on the outcomes of their work. A system in which REBs and research ethics policy-makers systematically assessed the outcomes of their decisions, especially from the perspective of included participants, would better serve a careful refinement and deployment of the concept of vulnerability in research ethics.

the identification and effective remediation of vulnerability may serve in and of itself as a barrier to research with groups typically considered to be vulnerable (e.g., prisoners, pregnant women, children, etc.) [60]. While care and additional scrutiny for research with participants in vulnerable circumstances is often warranted, the gatekeeping this entails can be paternalistic and may prevent "potential participants from speaking for themselves or exercising agency in their own right" [67, p.18]. Further, anticipation of difficulties with access and research ethics approval may cause researchers to avoid conducting research with these participants. This does not mean that the notion of vulnerability ought to be categorically. Instead, it underscores the need to reconsider both proposed responses to vulnerability themselves as well as the process through which responses can be identified and elaborated.

These four issues, of both conceptual and practical import, highlight the need for an account of vulnerability that captures what it is exactly about vulnerability that is ethically concerning and that lends itself to a process through which both research teams and REBs can identify and address vulnerability. The scholarly literature on vulnerability in research ethics has, in large part, been prompted by a fairly broad recognition of the existence of the above-cited debates and problems. So far, most refined accounts of vulnerability have focused on providing a better (or more comprehensive) account of the sources and types of vulnerability, deconstructing subpopulation, list-based approaches to offer elaborate typologies or taxonomies of vulnerability [33, 44, 50, 69]. Other authors have focused on delineating the normative reasons why vulnerability matters [4, 18, 20, 43] or on the sorts of duties and obligations researchers, REBs, and others may have to addressing vulnerability in research and, more broadly, in society [11, 22, 49]. However, few with the exception of Hurst's work on the concept of vulnerability (which we will discuss below) have offered a genuinely integrative and functional account of vulnerability that addresses all four debates arising in the literature and fewer still have operationalized the concept to make it a functional construct that can help guide researchers and REBs.

Four components of an integrative and functional account of vulnerability in research ethics

On our view, an integrative and functional account of vulnerability should include (1) a definition or description of vulnerability; (2) normative justifications; (3) applications; and (4) implications. Figure 1 explains these four components as well as how they relate to one another. The concept of vulnerability first designates a reality, further defined by its dimensions (i.e., key 'types' or 'sources'). The normative justifications explain why vulnerability matters from an

ethical perspective. The definition and dimensions, informed by the justifications, facilitate the identification of those to whom the concept applies. The immediate outcome of this iterative process of application is the generation of concerns, which specify both the 'how' or 'why' and the 'to what' elements of vulnerability. Finally, identification of these concerns prompts the development of implications tailored to the specific issues in question. These implications could be wide ranging and include the additional protections already suggested by research ethics policies and guidelines as well as measures designed to facilitate the meaningful participation of oft-excluded groups in research. The four major components of vulnerability must be internally consistent and must produce an account that can guide researchers, REBs, and others to understand and effectively address vulnerability in practice. The next section proposes an integrative and functional model that is enriched by previous accounts in the scholarly literature and captures these four components. Figure 1 further describes these components and illustrates their logical relationships to each other.

**Table 9 Basic components of the logical structure of an integrative and functional account of vulnerability.**



| Component | Justification and role | Utility and impact |
|---|---|---|
| Description (and dimensions) | Answers the questions:<br>• What is vulnerability?<br>• What types of vulnerability should we be concerned with? | • The central point of reference through which interpretation of the other elements can be guided and their coherence in the account as a whole can be assessed.<br>• Brings richness to the possible sources from which situations of vulnerability may stem. |
| Normative justifications | Answers the question:<br>• What ethical principles ground obligations to vulnerable participants? | • Facilitates the interpretation of the concept of vulnerability in its application to a situation at hand.<br>• Alerts us to the moral content of the concept, indicating what it is about vulnerability that generates duties or special obligations for researchers, REBs, and others in research. |
| Application | Answers the question: | • Facilitates the assessment of vulnerability, or the identification |

| | | |
|---|---|---|
| (and concerns) | • To whom does the concept apply and how? | of participants who may be in circumstances of vulnerability.<br>• Indicates the specific concern generated by the analysis or identification of vulnerability in a specific context. |
| Implications | Answers the question:<br>• What obligations are owed to vulnerable participants and how should these be enacted?<br>• How can the vulnerability of the participant tackled and mitigated? | • Allows for the identification of the relevant considerations and safeguards necessary to ensure that research involving participants in vulnerable circumstances in conducted in a fair and ethical manner. |

### Developing an integrative and functional account of vulnerability: A critical aggregative analysis of the literature

In seeking an integrative and functional account of vulnerability in research ethics, we turned to existing literature, which offers a number of relevant answers and insights but not within a single account that integrates the four required components. However, Hurst's (2008) widely-cited account is especially compelling, as it addresses the definition and normative justification of vulnerability, and provides a clear process for mapping the implications of vulnerability for researchers and REBs [18, 72]. Her description of vulnerability takes the form of what has been described as a "functional definition" [10, p.12]. A functional definition shows how a concept functions and relates to other concepts – in Hurst's case, to harms, wrongs, and normative claims. In contrast to functional definitions are content definitions, which "clarify the fundamental characteristics of vulnerability" [10, p.12]. Accordingly, we borrow much of her model to generate an integrative-functional account. In this section, we outline our model through the structure of the four components of vulnerability. For each component, we put forward our integrative proposal and outline how it builds on the accounts of Hurst and others.

*Description and dimensions of vulnerability*

We propose that vulnerability be understood as a situation in which a research participant has an identifiably increased likelihood of incurring additional or greater harm or wrong because of relational asymmetry in the research context (i.e., between participant and researcher, research environment, research institution). Hurst (2008) proposes that vulnerability as a claim to special protection should be understood as an identifiably increased likelihood of incurring additional or greater wrong, thus encompassing historical definitions of vulnerability (consent- and harm-based views). Her definition is narrow enough to encompass only research-relevant wrongs; the

wrongs of concern are "wrongful harms and the wrongs we incur when something to which we have a valid claim is denied us" [18, p.196]. However, it is broad enough to encompass the concerns expressed in other definitions across the literature. Macklin (2003), for example, argues that vulnerability refers to a susceptibility to exploitation [48], and Zion, Gillam, and Loff (2000) similarly propose that vulnerability is a greater chance of exploitation caused by a lack of basic rights and liberties [49]. On Hurst's view, these concerns are captured as an increased likelihood of incurring a greater wrong linked to unjust involvement in or benefits from research.

Despite encompassing a number of key concerns, Hurst's definition on its own lacks essential content regarding the nature of vulnerability itself. Hurst's functional definition of vulnerability allows for flexibility and facilitates a process of clear practical application and action guidance (which we will review below), but does not draw attention to the relational nature of vulnerability. The scholarly fuss over vulnerability is not only because it describes greater susceptibility to risk (physical, psychological, social, economic, and so on) [61] or even that the subject is incapable of protecting their interests *per se*, but also because the concept underscores that researchers could actively take advantage of this situation and stand to benefit from it. A look at some of the troubling events in the history of biomedical research plainly illustrates that the relational positioning of research participants combined with the self-serving and morally shallow justifications of researchers is the fundamental factor that renders them vulnerable to harm, wrong, or abuse. The sociopolitical context of both researchers and the researched is fundamental to this relational asymmetry and must be taken into account. In its current form, Hurst's account fails to call attention to important relational dynamics in the research environment that allow participants to be made vulnerable and it does not capture sufficiently the concerns that researchers can voluntarily or inadvertently take advantage of subjects.

The relational asymmetry central to vulnerability is better captured in a number of 'content definitions' of vulnerability [10], and we draw on and add to this work to further enrich Hurst's definition. Fischer (1999) and Schrems (2014) take an explicitly relational approach, informed by an ethics of care, and argue that vulnerability is a relational construct [4, 20]. For these authors, vulnerability refers to a participant's dependency on the researcher in the context of a specific research project. Schrems argues more specifically that vulnerability captures the relationship between "the health status of a person and the extent to which the individual is

dependent on the researcher and the research context" [4, p.838]. Bell et al. (2014) similarly argue that vulnerability captures a power asymmetry between participant and researcher team [3]. Taken together, these characterizations of vulnerability highlight the dependency and relative lack of power that can be experienced by research participants. Explicitly addressing the relational nature of vulnerability within Hurst's account implies that harm or wrong are not predetermined [20], and further emphasizes that vulnerability is not a feature of individuals themselves, but of specific situations [3, 4, 11]. As such, a central added value of adopting this approach is that it underscores that circumstances of vulnerability can be reduced, if not eliminated entirely, with careful and critical reflection on the research protocol and environment more broadly [3, 20]. Further, it uniquely (i.e., unlike other central concepts of research ethics) sensitizes researchers, including research staff, sponsors, and institutions, to their relational positioning in the research context and the potentially negative impacts this can have on participants if left unexamined and unaddressed.

Dimensions extend the description of the concept of vulnerability, sketching a landscape of the personal and social conditions in which participants can experience a relational asymmetry that increases their risk of harm or wrong. Otherwise stated, these could be conceived of as sources of vulnerability, and have been a central focus of a number of accounts in the scholarly literature [8] (see Table 10 for further details of the relevant accounts). Kipnis' taxonomy of vulnerability (2001; 2003), refined by Horn (2007), posits seven key types (and, by extension, sources) of vulnerability in research: cognitive, juridic, deferential, medical, allocational, infrastructural, and social [33, 51, 69]; these types can be thought of as dimensions of vulnerability. Hurst (2008) recognizes the importance of the sources of vulnerability, but provides little more than a cursory glance at the broad categories of these sources (i.e., characteristics of the participant, the research protocol, and the environment). As a result, her account again risks missing the crucial insight offered by the concept of vulnerability: that protocols, researchers, and research environments can inadvertently bring to the table to further deepen the potentially problematic dependency and relational asymmetry between participant and researcher/environment.

Taxonomic approaches to vulnerability have been critiqued on the grounds that assuming types and sources of vulnerability can be classified implies a fixed and rigid concept [11, 99]. More specifically, it has been argued that Kipnis' taxonomy implies that all those experiencing

the sources identified are vulnerable, and all those outside of these classes are not – potentially leading to false positives and negatives [24]. As such, we argue that these dimensions of vulnerability should be approached as dynamic, as layered, and as non-exhaustive of the concept of vulnerability. As other authors have highlighted, the interaction between personal, social, and environmental factors can create circumstances of vulnerability, and different types of vulnerability can interact with and compound one another. Luna (2009) in particular has put forward an influential account of a 'layered' notion of vulnerability. Luna argues that the identification of necessary and sufficient conditions results in too rigid a concept, which she believes must be understood dynamically and relationally. On her view, there is no solid and unique vulnerability, but instead there are different vulnerabilities that arise from different layers, as well as interactions between these layers; individuals themselves are not vulnerable, but a particular situation (in which features of their situation interact with those of the environment) can render them vulnerable [11, 73].

Drawing on a taxonomic approach to vulnerability need not entail a commitment to these dimensions alone. We recognize that other dimensions may arise, or that participants who may experience one or more of these dimensions may not actually experience an increased likelihood or additional or greater harm or wrong in research. However, adopting a more robust account of the dimensions of vulnerability can facilitate a deeper and more concrete understanding of this concept to researchers and, from a functional perspective, can improve researchers' and REBs' abilities to diagnose and respond to vulnerabilities in research. Attuning these stakeholders to some major dimensions of vulnerability and to the manner in which these can interact and impact the presence of vulnerability in a particular research project further reinforces its relational nature and the notion that vulnerability will, in general, be amendable to remediation.

**Table 10 Accounts from the scholarly literature focusing on the types and sources of vulnerability.**

| Account | Structuring concept | Key contributions | Key strengths | Key weaknesses |
|---|---|---|---|---|
| Kipnis (2003); see also Horn (2007), who proposes slight changes to Kipnis' terminology as adopted here | Taxonomy of vulnerability | • Cognitive: lack of capacity to deliberate and make participation decisions about a given study.<br>• Juridic: liability to the authority and influence of others who may have an independent interest in that participation.<br>• Deferential: custom to deferential | • Clear identification of distinct sources of vulnerability.<br>• Types of vulnerability can be | • Relates vulnerability singularly to consent, leaving out other wrongs of concern.<br>• Does not |

| | | | | |
|---|---|---|---|---|
| | | <ul><li>behaviour that may make participation refusal difficult.</li><li>Medical: participant selection based on a serious health condition for which no other satisfactory treatments exist.</li><li>Allocational: research participation will provide access to benefits participants could not otherwise access.</li><li>Infrastructural: a political, organizational, economic, and social research context that does not possess the integrity and resources needed to manage the study.</li><li>Social: participant a member of a group whose rights and interests have been socially disvalued.</li></ul> | <ul><li>cumulated.</li><li>Avoids sub-population approach.</li></ul> | <ul><li>clearly capture relational aspects of vulnerability.</li><li>Does not distinguish between intrinsic and extrinsic sources of vulnerability.</li></ul> |
| Luna (2009); see also Luna and Vanderpoel (2013) | 'Layered' approach to vulnerability | <ul><li>Luna argues that there is no solid and unique vulnerability and thus does not identify specific sources or types. She argues that vulnerability is relational, and stems from the relationship between persons and groups and their circumstances or contexts. As such, Luna proposes an approach to thinking about the sources and types of vulnerability as 'layers' which can interact with and influence one another.</li></ul> | <ul><li>Clearly captures the relational and dynamic nature of vulnerability.</li><li>Draws attention to the important analytic role of vulnerability.</li></ul> | <ul><li>Does not clearly generate obligations for REBs, researchers.</li><li>Lacking guidance for the practical application of the account.</li></ul> |
| Meek Lange, Rogers, and Dodds (2013) (also discussed in Rogers, Mackenzie, and Dodds 2012) | Typology of the sources of vulnerability | The sources of vulnerability can be: <ul><li>Inherent: stem from the human condition, e.g. our corporeality, neediness, or dependence on others.</li><li>Situational: stem from the environment and are context-specific, e.g. one's personal, political, or social situation.</li><li>Pathogenic: a subtype of situational sources that arise from dysfunctional social or personal relationships, e.g., abusive relationships, politically unstable environment.</li></ul> These sources can be experienced as: <ul><li>Occurrent: immediate and present.</li><li>Dispositional: latent and background.</li></ul> | <ul><li>Clearly captures the relational and dynamic nature of vulnerability.</li><li>Identifies categories of sources of vulnerability that can guide researchers and REBs in their assessment.</li></ul> | <ul><li>Not clear how (from a normative stance) obligations arise.</li><li>Lacks a clear process for the application of this account to the research context.</li></ul> |
| Rogers and Ballantyne (2008) | Intrinsic and extrinsic vulnerability | Vulnerability can be: <ul><li>Extrinsic: due to external circumstances and derive from participants' socioeconomic contexts</li><li>Intrinsic: due to features of the individuals themselves, e.g., their age or medical condition</li></ul> | <ul><li>Clear identification of distinct sources of vulnerability.</li><li>Captures more dynamic</li></ul> | <ul><li>Not clear how (from a normative stance) obligations arise.</li><li>Lacks a clear process for</li></ul> |

| | | | | factors which can act as sources of vulnerability | the application of this account to the research context. |
|---|---|---|---|---|---|

*Normative justifications of vulnerability*

On our view, normative justifications of vulnerability stem both from established and widely-accepted principles of research ethics (e.g., respect for persons, concern for welfare, and justice), as well as from the recognition of potentially problematic relational asymmetries within the research context. It is critical to recognize different justifications for the ethical relevance of vulnerability and that it is not necessary to rely on only one. As argued above, not explicitly identifying the normative underpinnings can lead to confusion and a lack of coherency between the key components of vulnerability and can impede the interpretation and application of ethical guidelines in one's specific context. As such, delineating the multiple sources of normative justification highlights the range of concerns it should encompass and brings richness to the concept of vulnerability.

By building on Hurst's concern for increased or additional harms or wrongs, we adopt some aspects of her arguments for the moral underpinnings of the concept of vulnerability. Hurst argues that vulnerability is not itself an ethical principle and does not generate any new moral obligations in the research context. Instead, she argues that the normative justification of the implications of vulnerability stems from widely-accepted, existing principles of research ethics. Vulnerability does not require a special kind of ethical scrutiny, but an especially high degree of care for the sorts of ethical criteria typically considered (e.g., harm, unfair distribution of risk and benefits, or faulty consent). We accept this acknowledgment of the high degree of care for the general principles of research ethics that the functional-integrative account of vulnerability generates, but in acknowledging the relational nature of vulnerability we emphasize that moral obligations to address vulnerability arise within a context of dependency [20]. The central contribution of the concept of vulnerability in research ethics (i.e., amongst the other principles and concerns of research ethics) is its capacity to to sensitize researchers about their own position with respect to the relational asymmetry that they find themselves in with regards to research subjects. As such, recognizing researchers' asymmetrical obligations to relieve the risks and wrongs associated with dependency and to protect subjects' interests in light of this

dependent relationship fulfills a vital contribution of the concept of vulnerability amongst the other considerations of research ethics .

*Application and concerns of vulnerability*

The application of vulnerability requires careful consideration of how the definition and normative justifications bear on specific participants within the context of a given research project, with respect to their fundamental interests in research. Understanding who is vulnerable is thus not a matter of checking a list of vulnerable groups but of turning a careful and critical eye to factors brought by participants, researchers, and institutions, and the broader socioeconomic environment in which these actors are situated. This proposal is in line with the views of a growing number of scholars who argue that the application of vulnerability should not take the form of a subpopulation approach.

Luna (2009) and Lange et al. (2013), key proponents of a dynamic approach to vulnerability, suggest broadly that it can only be assessed by looking at individuals in context [11, 22]. However, they do not provide clear, functional guidance for the application of their accounts of vulnerability. A key advantage of Hurst's account is that she provides a process through which researchers and REBs can assess vulnerability. To identify vulnerability in research, Hurst suggests that researchers and REBs start by identifying the sorts of harms or wrongs likely to occur in a given research protocol, and then identify any participants at predictably more at risk of incurring this wrong. The integrative-functional account's approach to applying (i.e., identifying) vulnerability in research entails considering the dimensions of vulnerability as they relate to the possibility of increased or additional wrongs in the context of a specific research project. The types of wrongs of concern in research can be assessed by drawing on Emanuel et al.'s (2003) framework of the seven requirements for ethical research: social or scientific value, scientific validity, fair subject selection, favorable risk-benefit ratio, independent review, informed consent, and respect for potential and enrolled subjects [18, 104]. Within each requirement, researchers and REBs can consider which dimensions of vulnerability may be of concern. For example, a researcher considering ethical issues in the design of a clinical research project would consider whether participants would be likely to experience any wrongs related to the social or scientific value of the project relating to any cognitive, juridic, deferential, medical, allocational, infrastructural, or social form of vulnerability [33, 51, 69].

Identifying concerns is an immediate outcome of the application of vulnerability and, as will be discussed in the next section, addressing the implications of vulnerability requires an understanding of the specific domains and wrongs in question. These concerns effectively result from the interplay between the dimensions of vulnerability and the key criteria of ethical research. For example, a lack of decision-making capacity may signal a cognitive vulnerability that could cause a participant to be unable to adequately understand and make an informed decision about their research participation.

*Implications of vulnerability*

The implications of vulnerability will depend specifically on the wrong and the domain of vulnerability in question, and a number of strategies implemented by different actors may be required within a single research project. The accounts of a number of other authors [3, 11, 18, 22, 33, 69, 72, 73] also contend that who has a role in responding to vulnerability and what form that response should take is contingent on relevant factors within a specific research context. Hurst (2008), for example, argues that responses must be tailored to the wrong in question and suggests that Emanuel et al.'s (2003) framework can be used to map implications. What the integrative-functional account adds through the process of application is a more thorough and enriched assessment of participant vulnerability, facilitating the development of tailored and targeted strategies for its remediation. Further, in light of the recognition of the fundamentally relational nature of vulnerability and explicit orientation towards the contributions of researchers and research environments to exacerbating dependency and relational asymmetry, these measures will also depend on the dimension of vulnerability and the relationship between researcher and source of vulnerability. For example, in the Canadian context, a non-Aboriginal researcher working for the federal government (e.g., Health Canada) and intending on doing research in collaboration with an a community of Aboriginal people would need to be mindful of how his employer and his own personal background represent for this specific community [105]. In this case, the legacy of treatises disregarded by the British Crown and the Canadian Government combined with decade-long racist and xenophobic federal policies may form a backdrop of well-founded suspicion on behalf of the research participants. Understanding the source of a relational asymmetry would, in this case, be relevant to determining the terms of a

fair agreement and of measures to restore a sense of reciprocal relationships where participants would not feel they are misled and taken advantage of [105].

Application and illustration of an integrative-functional enriched account of vulnerability

The application of the functional-integrative account aligns with, and is well-supported by, a pragmatist approach to research ethics [86]. The most relevant features of such an approach for our account are a "conceptualization of ethical principles… as a set of working hypotheses", an emphasis on "open-minded engagement of ethical inquiry with the specific contextual details" of a research project, "[a]cknowledgment of the fallibility of principled judgments about clinical research" and of the need to revise "assumptions, decisions, and policies based on new information and analysis", and "[t]he importance of open-minded debate and deliberation, as well as respect for minority viewpoints, amongst a diversity of individuals" involved in the review of ethical research [86, p.25-26]. The integrative-functional account of vulnerability treats researcher or REB intuitions about or research ethics guidelines on the vulnerability of specific groups as working hypotheses that can be tested through a systematic analysis of dimensions and wrongs. As an analytical tool, the integrative-functional account facilitates a finer-grained analysis of the potential vulnerability of participants in a specific research context. It is not intended to generate summative conclusions regarding the overall vulnerability (or not) of a specific group. Instead, this account can bring more rigour and thoroughness to what otherwise may be unchecked assumptions about the vulnerability of subpopulations of participants. In this section, we sketch the method for applying the integrative-functional account of vulnerability to a research context in which participant vulnerability has typically been a concern: deep brain stimulations (DBS) for the treatment of treatment-resistant depression (TRD). While an in-depth analysis of vulnerability in this context is beyond the scope of this paper, we will illustrate how this account can facilitate a systematic analysis of the research context for matters related to vulnerability. Further, it can increase the accuracy of the identification of specific concerns and allow for the development of tailored responses to the dimensions of vulnerability involved/of concern consistent with the pragmatist standpoint referenced earlier.

DBS is a minimally invasive neuromodulation technique that involves the stereotactic implantation of uni- or bilateral electrodes in specific brain structures [106]. These electrodes are connected to a battery-powered neurostimulator which is permanently implanted in the

infraclavicular region [106]. DBS is an accepted intervention for some severe, treatment-resistant neurological and medical conditions, such as Parkinson's disease and dystonia and is currently being trialed for its safety and efficacy in the treatment of a range of psychiatric conditions, including TRD [106, 107]. It is estimated that 30% of patients with major depressive disorder do not respond adequately to established pharmacological, psychotherapeutic, or somatic treatments [106]. After insufficient response to 2 or more adequate treatments, these patients are described as having TRD, a condition that is associated with illness chronicity, reduced quality of life, and a higher risk of suicide [106, 108].

In the context of research on the use of DBS for TRD, concerns are often raised about the vulnerability of these persons with TRD [107, 109], stemming from a presumed lack of capacity to consent. Protections to remediate this perceived vulnerability focus on stricter processes of informed consent often including capacity assessments for any potential participant [3]. While evidence does not support a categorical assumption of impaired capacity in the context of TRD [3, 6, 107], there are other features of this context that could be of concern. For example, the risks of this invasive procedure, largely unknown benefits, issues of unwarranted hope and hype generated by a broader social narrative about DBS, and the difficult situations of the patients themselves, characterized by failed treatments, debilitating symptoms, and chronic illness, could generate concerns in the research context [106-113].

Applying the integrative-functional account of vulnerability begins with a heuristic-like initial review of the seven dimensions of vulnerability to consider which may be relevant. This step serves to 'sense' if there are any relevant dimensions of vulnerability at stake in a research protocol. Further, it brings more specificity to the current open-ended questions about the vulnerability of research participants voiced in research ethics guidelines. At the same time, this should remain a rather quick determination made based on available information, including relevant regulations and international norms (see Table 11), and the good judgment of those involved in ethics review. If there is a suspicion that the participants may be vulnerable with respect to at least one of the dimensions, there is then a need to 'cross-check' the dimensions thought to be of relevance with the criteria for ethical research [104], which establish which potential wrongs are of relevance to research [18]. This cross-checking will facilitate the identification of concerns and, as such, the development of targeted responses. Table 12 illustrates what this process might look like in the context of DBS for TRD.

**Table 11 Potential vulnerabilities of persons with TRD according to international research ethics standards and the corresponding dimensions of concern.**

| Relevant subgroup | Policies/ Guidelines | Explanation (where provided) | Corresponding dimensions of vulnerability |
|---|---|---|---|
| Persons in existing relationship with investigators | <ul><li>CIOMS</li><li>ICH GCP</li><li>National Statement</li></ul> | <ul><li>Voluntary consent may be compromised by expectations of benefit or repercussions or authority of one party over another.</li></ul> | <ul><li>Deferential</li><li>Juridic</li></ul> |
| Persons with mental illness or mental health problems | <ul><li>Clinical Trials Regulation</li><li>National Statement</li><li>TCPS2</li><li>Research Governance Framework</li></ul> | <ul><li>Have historically been treated unfairly in and excluded from research.</li><li>Vulnerable to various forms of discomfort and stress.</li><li>May face difficulties understanding the research project as well as the roles and responsibilities of those involved.</li></ul> | <ul><li>Cognitive</li><li>Social</li><li>Medical</li></ul> |
| Persons with serious diseases | <ul><li>CIOMS</li><li>Belmont Report</li></ul> | <ul><li>May be treated with drugs or therapies with unproven safety and efficacy.</li><li>May be readily available as research subjects.</li><li>May be easy to manipulate.</li></ul> | <ul><li>Medical</li><li>Deferential</li><li>Juridic</li></ul> |

**Table 12 Application of the integrative-functional account of vulnerability in the context of DBS for TRD.**

| Criterion for ethical research and description | Relevant dimension(s) | Concern | Possible implication(s) |
|---|---|---|---|
| **Value:** enhancements of health or knowledge must be derived from research | • Social | • Historical lack of access to benefits or knowledge derived from research may unduly motivate invasive research [114, 115]. Further, persons with mental illness may be excluded from defining what research is valuable to them, including whether an invasive intervention is of value. | • Encouraging community engagement in the development and design of research, especially regarding the value of the research question itself (i.e., the proposed intervention). |
| **Scientific validity:** the research must be methodologically rigorous | • Medical | • There is a lack of understanding of underlying mechanisms of TRD, as well as of DBS, contributing to significant debate over the appropriate target(s) for stimulation in this context. This may impede rigorous research [106, 111, 113]. | • Evidence from preclinical trials, rationale, and justification should be carefully examined. In some cases, research with humans may not yet be justifiable (i.e., due to lack of scientific validity stemming from lack of preclinical research). |
| **Favourable risk-benefit ratio:** within the context of standard clinical practice and the research protocol, risks must be minimized, potential benefits enhanced, and the potential benefits to individuals and knowledge gained for society must outweigh the risks | • Infrastructural | • DBS is the most invasive psychiatric intervention and surgery comes with side effects. For example, rare but severe first effects (i.e., related to the surgery itself) include risks of seizure, bleeding in the brain, and infection, neurological impairment, or death [106, 110].<br>• Second effects (i.e., related to the stimulation) can be reversed and can include hypomania and anxiety [106]. Psychosocial risks can include changes to personality which can impact personal relationships and self-identity [106].<br>• Given the limited use of DBS in TRD this procedure also carries a significant degree of unknown emotional, | • A risk reduction approach should be taken, ensuring evidence of consideration of both the foreseeable risks and plans for their management, as well as the long-term, unknown risks. Follow-up and involvement of a number of specialized health professionals will be required to support the participant as long as they have the device (i.e., after the 'end' of the study) [106, 109] to minimize harms. Recognition and planning for management and support of participants for the long-term must be evidenced. |

| | | | |
|---|---|---|---|
| | | cognitive, and behavioural consequences [107, 111]. | |
| | | • Small, open-label, uncontrolled studies have shown up to 50% reduction in TRD symptom severity at various targets. The potential benefits are widely considered to be unclear [106, 107]. | |
| **Independent review:** unaffiliated individuals must review the research and approve, amend, or terminate it | • Infrastructural<br>• Social | • Stereotypes and assumptions abound about the characteristics and capacities of persons with TRD (as with mental illness more broadly) [3, 25, 107]. If left unchecked, they could impede effective review.<br>• DBS is a highly specialized procedure, and effective review will require expertise on DBS and regarding TRD. | • Outside (unaffiliated) expertise should be sought as required, perhaps including involvement of a member of the target population. |
| **Informed consent:** individuals should be informed about the research and provide their voluntary consent | • Cognitive<br>• Medical<br>• Deferential<br>• Infrastructural | • The presence of TRD does not necessarily entail a lack of decision-making capacity [3, 21, 25]. However, other factors may be relevant in considering constraints on voluntary and informed decision-making, including a history of a demoralizing and often severely disabling disease, repeated failed treatments, and the unfounded media 'hype' surrounding DBS that may unduly influence patients' perceptions of risks and benefits [110, 116, 117].<br>• Given the seriousness of the procedure, the need for long-term, multidisciplinary follow-up, the repeated surgeries that will be required to replace the stimulators battery packs (every 6 months-5 years), and so on, DBS is a very involved, certainly life-altering treatment. Not only will patients need to be committed to the plan and appreciate the long-term care | • Patient and family (or other social support)'s expectations need to be actively and continually assessed and managed. Active education about the known risks and benefits of DBS (emphasizing the significant unknown risk) is warranted. Further, recognizing that many will seek out their own information online, accurate and reliable resources should be provided [116, 117].<br>• A much more thorough consent process than would be adopted in a typical trial is warranted in this context. Investigators could adopt an 'interview-style' consent process, individualizing the discussion to address patients' and families' specific questions, probing motivations and potential misperceptions, and taking as much time as needed (e.g., could be discussed over multiple appointments) [107].<br>• In both education and consent strategies, use of unaffiliated educators could mediate potential effects of any sense of duty or obligation patients and families may feel to researchers |

| | | it involves, but their family members (and/or other social support systems) will need to be involved as well [110, 116]. Without the infrastructure to support a thorough, involved information and consent process, patients and their families may not be well-supported in making such a complex decision. | with whom they may have a longstanding and positive relationship [117]. |
|---|---|---|---|
| **Respect for potential and enrolled subjects:** subjects should have their privacy protected, the opportunity to withdraw, and their well-being monitored | • Deferential | • Participants may feel restricted in their ability to withdraw given the significant investment of time and resources DBS entails, a desire not to negatively impact the therapeutic relationship or to lose access to their specialists, or simply due to the relational asymmetry inherent in the physician-patient relationship [5]. | • Potential participants should be actively educated about their rights and given access to unaffiliated patient advocates who can check in about their experiences in the trial, assess their desire to remain enrolled, etc. |

As Table 3 illustrates, single dimensions of vulnerability may be relevant to multiple criteria for ethical research. For example, the potential social vulnerability of persons with TRD generates concerns with regards to the criteria of 'value' and 'independent review'. It is important to note that conclusions about the dimensions and potential research wrongs of relevance ought to be based on evidence, and will also require open, informed discussion within research teams and REBs, as well as eventually between these groups. The generation of specific vulnerability-related concerns through the integrative-functional account means that remediation can be tailored to both the 'source' of the vulnerability and the potential wrong in question.

The analysis entailed by the integrative-functional account requires attention to context, open-minded engagement of a number of perspectives, and the revision of assumptions about vulnerability when the evidence suggests otherwise. This pragmatist approach to research ethics and vulnerability may in some cases call for the revision of guidelines and policies (e.g., unfounded statements about the categorical vulnerability of certain groups). It may also call more broadly for the revision of some of the fundamental practices of research ethics; for example, the call for openness to revising assumptions, policies, and so on based on new information also entails a need to gather relevant information. In the case of policy on vulnerability, this would include assessing whether proposed protections meet their stated aims. At the same time, the pragmatist approach also highlights that the functional-integrative account can be applied in the context of existing research ethics governance. Treating the vulnerability-related claims of these guidelines as hypotheses would entail that a suggestion that group X is vulnerable and in need of special protections would prompt analysis through the functional-integrative account to determine how they might be vulnerable and what, exactly, they might be vulnerable to. There may be more or less flexibility depending on the specific regulatory context in which the research is proposed but, in general, the broadness of most research ethics guidelines seems to invite a pragmatist approach to moral problem solving [71, 86].

Concluding Remarks

Protecting vulnerable participants is a central function of research ethics which may be impeded by the conceptual gaps in current research ethics policies and guidelines. In this article we have argued for an integrative and functional account of vulnerability enriched by existing scholarly proposals about the meaning, justification, application, and implications of

vulnerability. This account can serve as an analytic tool for researchers, REBs, and others, facilitating a systematic assessment of the research environment for vulnerability-relevant concerns and the development of targeted implications. Drawing from a pragmatist approach to research ethics, we illustrated how the integrative-functional account may generate evidence-based guidance for responding to vulnerability. In this vein, we argue that our account (and, indeed, any account of vulnerability in research ethics) requires further validation from stakeholders, including researchers and REBs, regarding its utility in practice. Additionally, we recommend post-application validation of the implications generated by the account in a specific context to assess whether they did, in practice, prevent additional wrongs and harms from befalling research participants.

**Chapter 6: Discussion and conclusion**

<u>Discussion</u>

In this thesis, the concept of vulnerability has been explored within two interrelated bodies of literature: the policies and guidelines intended to guide researchers, REBs, and other stakeholders in the design, review, and conduct of ethical research, and the academic literature exploring vulnerability responding to problems and concerns generated by the policies and guidelines. In Chapter 2, the notion of vulnerability and its emergence in the history of research ethics was explored. An overview of central critiques of and debates surrounding this concept revealed three major areas in need of further clarification and exploration: the definition, justification, and application of vulnerability. Drawing from elements of the pragmatist approach to bioethics inquiry and the methodologies outlined in Chapter 3, Chapters 4 and 5 critically assessed the concept of vulnerability in the guidelines, policies, and scholarly literature on vulnerability in research ethics, focusing specifically on the aforementioned three major areas of vulnerability, as well as the implications of vulnerability, an additional area of interest identified in Chapter 4.

The results presented in Chapter 4 demonstrated that policies and guidelines may, on the whole (i.e., across the body of policies and guidelines), provide a richer account of vulnerability than suggested by some of the critiques within the academic literature. A wide range of intrinsic and extrinsic sources of vulnerability were identified, and it was suggested both implicitly and explicitly that vulnerability may exist on a spectrum and take different forms (and correspond to different ethical concerns) for different groups. However, we also found important gaps relating especially to the definition and justification of vulnerability. Few policies explicitly defined the concept or the ethical concerns in which it is grounded. Further, at the level of individual policies and guidelines this results in gaps that may result in a concept of vulnerability that is not very guiding for research stakeholders.

In Chapter 5, we critically reviewed the academic literature on vulnerability in research ethics and found that while important insights on the components of vulnerability have been proposed, no one account has integrated these to produce practical guidance for researchers, REBs, and others involved in the practices of research ethics. As such, we proposed an integrative (i.e., of the 4 central components of vulnerability) and functional (i.e., for researchers, REBs, and other research stakeholders) account of vulnerability in research ethics enriched by insights from the academic literature. Our integrative-functional account positions vulnerability

as an analytical tool that can facilitate a thorough analysis of the research context to identify factors that can render participants at greater risk of harm or wrong, and that allows researchers and REBs to develop targeted responses to the sources and wrongs/harms in question. Further, it encourages a reliance on evidence in making judgments about vulnerability in research ethics, and critical attention to the assumptions and stereotypes that may underlie designations of vulnerability within the research ethics guidelines, policies, and practices of REBs and others.

A broad goal of this thesis was to bring further clarity to the concept of vulnerability in research ethics and critically assess its conceptualization and operationalization in current research ethics thinking. Taken together, the results of Chapters 4 and 5 highlight a number of themes and broader implications which will be explored in this chapter. First, I will discuss the link between Chapter 4 and 5, and address how the integrative-functional account of vulnerability can be applied to support research ethics practice within the current landscape of research governance. Next, I will discuss the need for stakeholder-engaged, evidence-based research ethics, particularly with respect to the concept of vulnerability. Finally, I will further articulate how a pragmatist approach to research ethics governance and inquiry can support a more balanced approach to vulnerability and the goals outlined in the two preceding sections.

*The integrative and functional account of vulnerability within current systems of research ethics governance*

Uniting the two manuscripts presented in Chapters 4 and 5 is, of course, their focus on the concept of vulnerability in research ethics. Each entails a level of critical analysis of the current definition, normative justifications, applications, and implications of vulnerability within the policies and guidelines as well as the academic literature. However, the integrative and functional account of vulnerability should also be thought of as a tool to help stakeholders (e.g., researchers, REBs, and others concerned with vulnerability in research) navigate the gaps and issues identified within the current system of research ethics governance and oversight. Take, for example, our finding that most policies rely on listing groups of vulnerable participants without addressing the definition of vulnerability itself (i.e., what it means to say that a certain group is vulnerable). In the absence of a definition of vulnerability or an explanation for the vulnerability of a particular group, the integrative-functional account would facilitate an analysis of the situation of the participants and research context in question to determine whether the listed group is, indeed, at greater risk of harm or wrong, what they are vulnerable to, and why they

might be vulnerable in the context of this specific research project. This would also allow for the development of strategies for the remediation of vulnerability; the implications outlined within the policies and guidelines were generally broad, so the integrative-tailored account could help with their refinement and application to the unique research project and participant group in question. This does not mean, however, that our account endorses the status quo policy approach to vulnerability. As outlined in Chapters 4 and 5, and as will be further discussed in the next section, careful scrutiny and iterative refinement of these documents is required. In the interim, the integrative-account can address the real, on-the-ground needs of researchers and REBs and, hopefully, lead to better outcomes for research participants in situations of vulnerability.

*The need for evidence-based, participant-engaged research ethics*

As Chapters 2, 4, and 5 demonstrated, the appropriate meaning and use of the concept of 'vulnerability' in research ethics has been widely debated and heavily critiqued. This prompts the question: why do we, or ought we, hang on to the concept of vulnerability in research ethics? Some authors have argued that the notion of 'vulnerability' is not, in and of itself, a useful or relevant concept in research ethics. For example, Kottow (2003, 2004) argues that 'vulnerability' is a purely descriptive term, referring to an "essential attribute of mankind" which requires our acknowledgement but little else. He argues that we should instead be concerned with 'susceptibility' in research ethics, which better captures the external conditions that put people at risk of harm. 'Susceptibility', unlike the purely descriptive 'vulnerability', is a specific and accidental condition to be diagnosed and treated [118, 119]. Wrigley (2014) similarly argues that vulnerability is not a substantive concept because it has to be supported by, and generates content only through, other readily available concepts such as 'harm' or 'wrong'. However, he acknowledges that vulnerability is widely appealed to in research ethics and could be retained for its important practical linguistic function as a flag for other contextually determined issues [95].

As we showed in Chapter 5, a number of authors agree that vulnerability is an important analytical tool in bioethics. Indeed, the integrative-functional account proposes that vulnerability may serve as a unique lens through which researchers, REBs, institutions, and others can examine relation asymmetries in the research environment and the impact these can have on potential research participants. However, the meaning and function of vulnerability in research ethics is much more than a conceptual debate. These issues can, and ought to be, explored from

an empirical perspective, within a paradigm of evidence-based, stakeholder-engaged research ethics. There are significant knowledge gaps regarding the actual impact of the concept of vulnerability on research ethics thinking and practices, whether the protections and considerations proposed address issues of concern, and on the perspectives and experiences of participants deemed vulnerable themselves in research, and addressing these is necessary in order to improve both theory and practice relating to vulnerability in research ethics.

The need for evidence-based, participant-engaged research ethics has been articulated by a number of scholars recognizing this crucial gap in the field [3, 6, 120-129]. The notion of evidence-based ethics is modelled on evidence-based medicine [120, 124], which is defined as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" [130, p.71]. Evidence-based research ethics, then, calls on us to "seek the best evidence we reasonably can on the effects of research on human participants and exercise the responsibility to use that evidence to achieve the ethical objectives" of research ethics [120, p.6]. Even in the absence of this growing emphasis on evidence-based research ethics, it seems to make intuitive sense that ensuring research participants are properly protected would entail assessing the outcomes and impacts of the policies and guidelines designed to meet this goal. However, current systems of governance in North American fail to systematically assess the performance or outcomes of research ethics [120, 121, 131]. Further, while recent years have seen an increase in empirical research on human research ethics [120, 125], "most of the discourse around human participant protection has focussed on norms – rules, regulations, and governance arrangements—rather than on the actual effectiveness of these norms in achieving their ends—protecting participants from undue risk and ensuring respectful treatment as well as advancing the generation of useful knowledge" [120, p.1].

Along with this call is also one for a research ethics that is informed by, and engages with, its stakeholders, particularly persons who have participated in or may serve in the future as research subjects. Governance bodies often seek written feedback from the broader community on proposed research ethics policy changes. For example, in drafting the second version of the Canadian Tri-Council Policy on ethical research with human subjects, the Interagency Advisory Panel on Research Ethics (PRE) sought public comments on draft guidelines [132]. The concept of vulnerability received special attention in this revision process from a working group who proposed moving towards a dynamic and contextual understanding of this concept, adopting, for

example, the language of "vulnerable persons or groups" over "vulnerable populations", and stating that persons ought not be considered vulnerable in the basis of group membership alone [133]. There is little doubt that consulting the community of researchers and experts whose work is guided by a specific document is an important step in its revision. However, feedback is rarely sought from human research participants – the people whose experiences have motivated the need for research ethics guidelines to begin with. Instead, there is a reliance on speculation about abstract future subjects [134]. Indeed, the authority to define a given group as vulnerable has historically lain not with that group but with policymakers [135], and the legitimacy of the paternalism of research ethics is often taken for granted [136]. In a striking example, Gustafson and Brunger (2014) report their research ethics review experiences in a feminist participatory action research study with persons with disabilities. The REB judged the community as vulnerable and in need of protection, while "the disability community regarded itself as capable of making informed choices about the degree of risk that participation might involve" [135, p.998]. Engaging members of so-called vulnerable populations about their perceived vulnerability would represent a radical but important shift in our approach to this topic. Not only would engaging participants about their experiences and perspectives on research ethics guidelines fill a key knowledge gap about the impact of our practices, but "engaging potentially vulnerable research participants in the development of the policies and protections applied to them could ultimately remediate some aspects of their vulnerability (e.g., asymmetries of power compounded by the research environment)" [6, p.3].

Our work could be said to represent the focus on guidelines and norms that is the status quo in research ethics [120]. However, by bringing much-needed clarity and structure to the problems with current approaches to vulnerability and proposing an enriched account, we have also highlighted important paths for future research and tools for current, on-the-ground issues in the design and review of ethical research. Moving towards an evidence-based, participant-engaged refinement of the concept of vulnerability will require an examination of perspectives of participants (past and future) on the definition of vulnerability itself (e.g., drawing on the dimensions of the integrative-functional account) and experiences of feeling vulnerable in the research context, on what additional protections, considerations, or measures may improve their research experience, and on the broader mechanisms that could empower them in the research context (e.g., education about the research process itself and active involvement in the upstream

design of research). In the model of a "virtuous learning loop" [137], this research would feedback into research ethics practice, the impact of new or refined practices would be evaluated, and so on, in an iterative process of the refinement of current approaches and the development of new practices in human subjects research ethics [120].

*Pragmatism and a balanced approach to vulnerability and participant protection*

The problems with status quo approaches to vulnerability (outlined in Chapter 2), include that it may be too broad and too narrow, implying the need for a careful and balanced definition and application, as well as that it is, too often, detached from context. Chapters 4 and 5, as well as the preceding section of this chapter, highlighted a need for evidence and for stakeholder engagement regarding both theories and practices relating to vulnerability. Further, the integrative-functional account of vulnerability (presented in Chapter 5) stresses the need for open, context-driven deliberations amongst researchers, REBs, and others in discussions of vulnerability. Adopting an explicitly pragmatist approach to research ethics more broadly would support these goals, and a more balanced approach to vulnerability and participant protection. A number of scholars have described the central tenets of pragmatist approaches to bioethics [80, 82, 84, 101, 138, 139] and neuroethics [81, 140], highlighting their applicability to practical issues from clinical ethics to end of life issues [138]. Broadly, these scholars have highlighted the utility of context-driven, deliberative methods of inquiry for addressing concrete ethical issues and uncertainties in the clinical setting. As our exploration of vulnerability has shown, the practice of research ethics entails similar issues. REBs, for example, have to assess the ethical soundness of a project and potential vulnerability of participants on a case-by-case basis, interpreting and applying a variety of regulations and guidelines to each specific context [86]. However, there has been little discussion of the applicability of pragmatism to research ethics.

In their 2008 paper, Brendel and Miller make a plea for pragmatism in research ethics [86]. They argue that pragmatism can provide guidance both for the day-to-day functioning of the REB and for evaluation of overall policy standards and ethics guidelines [86]. Taking the need for scientific research and to protect human participants as the core tension of research ethics, they describe five major characteristics of a pragmatist approach to research ethics: (1) a focus on "case-by-case moral problem solving", (2) "[a] conceptualization of ethical principles in clinical research as a set of working hypotheses", (3) "[t]he need for open-minded

engagement… with the specific contextual details of proposed research projects, (4) "[a]cknowledgment of the fallibility of principled judgments… and of the appropriateness of revising basic assumptions, decisions, and policies based on new information and analysis", and (5) "open-minded debate and deliberation, as well as respect for minority viewpoints, amongst a diversity of individuals reviewing clinical research proposals" [86, p.25-26]. As illustrated in Chapter 5, such an approach aligns well with the use of the integrative-functional approach in the design and ethical review of research. Additionally, it supports the broader need articulated throughout in this thesis for an approach to research ethics that draws explicitly on empirical evidence, is malleable when the evidence points to a need for change in norms, policies, and practices, and emphasizes processes rather than outcomes alone.

Taking a pragmatist approach to vulnerability in particular could facilitate a shift towards a more balanced, context-specific identification of vulnerability, as well as the incorporation of undervalued voices into research ethics deliberations on this topic. As the earlier example from Gustafson and Brunger (2014) emphasized, while well-meaning REBs may view certain communities, of which their members may not be a part, as vulnerable and in need of protection, members of those communities may have a different perspective [135]. This underscores not only that the collective judgments of REBs may be based on stereotypes, but also that identity and group membership are fluid – any given participant will be a member of a multiple communities, and which aspects of their identity of group membership are relevant will change between contexts. However, given that REBs have a distant view of potential research participants, it is understandable that other relevant (i.e., potentially vulnerability-mediating) factors can be missed. Soliciting and giving weight to the perspectives of potential participants in the process of research ethics deliberations could work to counteract this issue. Of course, the feasibility of this strategy will depend on the research approach – for example, in feminist participatory action research, 'participants' are involved from the development of the research, whereas a privately-sponsored clinical trial would not have begun recruitment at the stage of research ethics review. However, this ought to be strived for using a variety of creative approaches to suit the research context at hand.

Limitations

This thesis reports the results of critical analyses of two major bodies of literature on the concept of vulnerability in research ethics: research ethics policies and guidelines and the academic literature. Limitations of our work include the common limitations of social scientific research, such as the possibility of the researchers' subjective input into the study design, questions, and data analysis. We attempted to address this issue and increase rigour by employing a team-based approach to coding and analysis. Additionally, our sampling was limited by the authors' language abilities, and the sample of research ethics policies and guidelines was limited to those with broad applicability adopted within Canada and countries with similar demographic and legal features. It is possible that vulnerability is conceptualized differently by different professions (e.g., nursing, where the emphasis on caring relationships with patients may influence this concept) or within different sociopolitical and cultural contexts. Future research could build on our work to explore and compare our results with those from policies and guidelines adopted within, for example, developing countries only, or those adopted by professional organizations or within more focused areas of research.

Conclusion

While the concept of vulnerability is widely employed in research ethics, especially in the ethics guidelines and policies that govern the conduct of research, it is considered vague and under-theorized and has been critiqued for its lack of utility in guiding researchers, REBs, and other stakeholders in the research process. In order to bring more clarity to this important concept, this thesis critically investigated the conceptualization and operationalization of vulnerability within the policies and guidelines that govern ethical research, as well as within the scholarly literature. We identified major conceptual gaps within the policies and guidelines (e.g., regarding the definition of vulnerability) which could negatively impact the applicability of the guidance on vulnerability for researchers and REBs. Turning to the academic literature for an account addressing these gaps, we filled a key gap by proposing an integrative and functional account of vulnerability enriched by insights from the academic literature.

Our work has brought further clarity to the concept of vulnerability in research, identifying clear gaps within the policies and guidelines and proposing a strategy for assessing

vulnerability in research. We have highlighted a need for further evidence-based, refinement of the concept of vulnerability, both in terms of its conceptual foundations and practical outcomes. While our work has advanced the discussion of vulnerability, there is now a crucial need for empirical research to assess and refine this important concept in research ethics.

## References

1. Corrigan, O. and R. Tutton, *What's in a name? Subjects, volunteers, participants and activists in clinical research.* Clinical Ethics, 2006. **1**(2): p. 101-104.
2. Jonas, H., *Philosophical reflections on experimenting with human subjects.* Daedalus, 1969: p. 219-247.
3. Bell, E., et al., *Beyond consent in research: Revisiting vulnerability in deep brain stimulation for psychiatric disorders.* Cambridge Quarterly of Healthcare Ethics, 2014. **23**(3): p. 361-368.
4. Schrems, B.M., *Informed consent, vulnerability and the risks of group-specific attribution.* Nursing Ethics, 2014. **21**(7): p. 829-43.
5. Ford, P.J., *Vulnerable brains: research ethics and neurosurgical patients.* The Journal of Law, Medicine, and Ethics, 2009. **37**(1): p. 73-82.
6. Bracken-Roche, D., E. Bell, and E. Racine, *The "vulnerability" of psychiatric research participants: Why this research ethics concept needs to be revisited.* The Canadian Journal of Psychiatry, 2016. **61**(6): p. 335-339.
7. Fisher, C.B., *A relational perspective on ethics-in-science decisionmaking for research with vulnerable populations.* IRB: Ethics & Human Research, 1997. **19**(5): p. 1-4.
8. Rogers, W., *Vulnerability and bioethics*, in *Vulnerability: New essays in ethics and feminist philosophy*, C. Mackenzie, W. Rogers, and S. Dodds, Editors. 2014, Oxford University Press: New York, NY. p. 60-87.
9. Schroeder, D. and E. Gefenas, *Vulnerability: Too vague and too broad?* Cambridge Quarterly of Healthcare Ethics, 2009. **18**(2): p. 113-21.
10. Ten Have, H., *Vulnerability: Challenging bioethics*. 2016, New York, NY: Routledge.
11. Luna, F., *Elucidating the concept of vulnerability: Layers not labels.* International Journal of Feminist Approaches to Bioethics, 2009. **2**(1): p. 121-139.
12. Cunha, T. and V. Garrafa, *Vulnerability.* Cambridge Quarterly of Healthcare Ethics, 2016. **25**(2): p. 197-208.
13. ten Have, H., *Respect for human vulnerability: The emergence of a new principle in bioethics.* Bioethical Inquiry, 2015. **12**(3): p. 395-408.
14. World Health Organization. *Environmental health in emergencies*. 2016 [cited 2016 June 26]; Available from: http://www.who.int/environmental_health_emergencies/vulnerable_groups/en/.
15. Guzie, G., *Vulnerability risk assessment. Technical Report ARL-TR-1045.* 2000, US Army Research Laboratory: White Sands Missile Range, NM.
16. Ho, C.W., A. Reis, and A. Saxena, *Vulnerability in international policy discussion on research involving children.* Asian Bioethics Review, 2015. **7**(2): p. 230-249.
17. Mackenzie, C., W. Rogers, and S. Dodds, *Vulnerability: New essays in ethics and feminist philosophy*. 2014: Oxford University Press.
18. Hurst, S.A., *Vulnerability in research and health care; describing the elephant in the room?* Bioethics, 2008. **22**(4): p. 191-202.
19. Luna, F., *'Vulnerability', an interesting concept for public health: The case of older persons.* Public Health Ethics, 2014. **7**(2): p. 180-194.
20. Fisher, C.B., *Relational ethics and research with vulnerable populations*, in *Research involving persons with mental disorders that may affect decisionmaking capacity. Volume II: Commissioned Papers.*, National Bioethics Advisory Commission, Editor. 1999, National Bioethics Advisory Commission: Rockville, MD. p. 22-49.

21.     DuBois, J.M., *Ethics in mental health research: Principles, guidance, and cases*. 2008, Oxford, NY: Oxford University Press.

22.     Lange, M.M., W. Rogers, and S. Dodds, *Vulnerability in research ethics: A way forward.* Bioethics, 2013. **27**(6): p. 333-40.

23.     Shaw, S., P.M. Boynton, and T. Greenhalgh, *Research governance: Where did it come from, what does it mean?* Journal of the Royal Society of Medicine, 2005. **98**(11): p. 496-502.

24.     Levine, C., et al., *The limitations of "vulnerability" as a protection for human research participants.* The American Journal of Bioethics 2004. **4**(3): p. 44-49.

25.     DuBois, J.M., et al., *Restoring balance: A consensus statement on the protection of vulnerable research participants.* American Journal of Public Health, 2012. **102**(12): p. 2220-2225.

26.     Schneider, C., *The censor's hand: The misregulation of human-subject research*. 2015: MIT Press.

27.     Levine, C., *Has AIDS changed the ethics of human subjects research?* Law, Medicine & Health Care, 1988. **16**(3-4): p. 167-73.

28.     Doucet, H., *L'éthique de la recherche: Guide pour le chercheur en sciences de la santé*. 2002: Les Presses de l'Université de Montréal.

29.     Rothman, D.J., *Strangers at the bedside: A history of how law and bioethics transformed medical decision making*. 1991: Basic Books.

30.     Hoeyer, K., L. Dahlager, and N. Lynöe, *Conflicting notions of research ethics. The mutually challenging traditions of social scientists and medical researchers.* Social Science & Medicine, 2005. **61**(8): p. 1741-9.

31.     Shuster, E., *Fifty years later: The significance of the Nuremberg Code.* New England Journal of Medicine, 1997. **337**(20): p. 1436-1440.

32.     Moreno, J.D., *Reassessing the influence of the Nuremberg Code on American medical ethics.* Journal of Contemporary Health Law and Policy, 1997. **13**(2): p. 347-60.

33.     Kipnis, K., *Vulnerability in research subjects: A bioethical taxonomy*, in *Ethical and Policy Issues in Research Involving Human Participants. Vol. II: Commissioned Papers and Staff Analysis*, N.B.A. Commission, Editor. 2001, National Bioethics Advisory Commission: Bethesda, MD.

34.     Brandt, A.M., *Racism and research: The case of the Tuskegee Syphilis Study.* Hastings Center Report, 1978. **8**(6): p. 21-29.

35.     Jones, J.H., *Bad blood*. 1993: Simon and Schuster.

36.     Beecher, H.K., *Ethics and clinical research*, in *Biomedical ethics and the law*. 1976, Springer. p. 193-205.

37.     Rubenstein, L.S., *Standards of accountability for consent in research.* Accountability in Research: Policies and Quality Assurance, 1996. **4**(3-4): p. 197-206.

38.     Sims, J., *A brief review of the Belmont Report.* Dimensions of Critical Care Nursing, 2010. **29**(4): p. 173-174.

39.     Childress, J.F., E.M. Meslin, and H.T. Shapiro, *Belmont revisited: Ethical principles for research with human subjects*. 2005, Washington, DC: Georgetown University Press.

40.     The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont report: Ethical principles and guidelines for the protection of human subjects of research*. 1979: Bethesda, MD.

41.	Rice, T.W., *The historical, ethical, and legal background of human-subjects research.* Respir Care, 2008. **53**(10): p. 1325-1329.

42.	Rogers, W. and M.M. Lange, *Rethinking the vulnerability of minority populations in research.* American Journal of Public Health, 2013. **103**(12): p. 2141-2146.

43.	Nickel, P.J., *Vulnerable populations in research: The case of the seriously ill.* Theoretical Medicine and Bioethics, 2006. **27**(3): p. 245-64.

44.	Rogers, W., C. Mackenzie, and S. Dodds, *Why bioethics needs a concept of vulnerability.* International Journal of Feminist Approaches to Bioethics, 2012. **5**(2): p. 11-38.

45.	Levine, C., *The concept of vulnerability in disaster research.* Journal of Traumatic Stress, 2004. **17**(5): p. 395-402.

46.	Bielby, P., et al., *Competence and vulnerability in biomedical research*. 2008: Springer.

47.	Koenig, B.A., *Have we asked too much of consent?* Hastings Center Report, 2014. **44**(4): p. 33-34.

48.	Macklin, R., *Bioethics, vulnerability, and protection.* Bioethics, 2003. **17**(5-6): p. 472-486.

49.	Zion, D., L. Gillam, and B. Loff, *The Declaration of Helsinki, CIOMS and the ethics of research on vulnerable populations.* Nature Medicine, 2000. **6**(6): p. 615-7.

50.	Rogers, W. and A. Ballantyne, *Special populations: Vulnerability and protection.* RECIIS: Electronic Journal of Communication, Information and Innovation in Health, 2008. **2**: p. S30-S40.

51.	Horn, L., *Research vulnerability: An illustrative case study from the South African mining industry.* Developing World Bioethics, 2007. **7**(3): p. 119-127.

52.	Eckenwiler, L.A., et al., *Hopes for Helsinki: Reconsidering "vulnerability".* Journal of Medical Ethics, 2008. **34**(10): p. 765-766.

53.	Goodyear, M., L.A. Eckenwiler, and C. Ells, *Fresh thinking about the Declaration of Helsinki.* British Medical Journal, 2008. **337**: p. a2128.

54.	Elliott, C., *The University of Minnesota's Medical Research Mess*, in *The New York Times*. 2015.

55.	Elliott, C., *The Deadly Corruption of Clinical Trials*, in *MotherJones*. 2010.

56.	Forster, H.P., E. Emanuel, and C. Grady, *The 2000 revision of the Declaration of Helsinki: A step forward or more confusion?* Lancet (London, England), 2001. **358**(9291): p. 1449-53.

57.	Solomon, S.R., *Protecting and respecting the vulnerable: Existing regulations or further protections?* Theoretical Medicine and Bioethics, 2013. **34**(1): p. 17-28.

58.	Dodds, S., *Depending on care: Recognition of vulnerability and the social contribution of care provision.* Bioethics, 2007. **21**(9): p. 500-510.

59.	Focquaert, F., *Rethinking Vulnerability.* American Journal of Bioethics Neuroscience, 2013. **4**(1): p. 44-45.

60.	Resnik, D.B., *Research subjects in developing nations and vulnerability.* American Journal of Bioethics, 2004. **4**(3): p. 63-4.

61.	Weijer, C., *Research involving the vulnerable sick.* Accountability in Research: Policies and Quality Assurance, 1999. **7**(1): p. 21-36.

62.	Rogers, W. and A. Ballantyne, *Justice in health research: What is the role of evidence-based medicine?* Perspectives in Biology and Medicine, 2009. **52**(2): p. 188-202.

63.	Dresser, R., *Wanted: Single, white male for medical research.* Hastings Center Report 1992. **22**(1): p. 24-9.

64.     Hutchins, L.F., et al., *Underrepresentation of patients 65 years of age or older in cancer-treatment trials.* New England Journal of Medicine, 1999. **341**(27): p. 2061-7.

65.     Murthy, V.H., H.M. Krumholz, and C.P. Gross, *Participation in cancer clinical trials: Race-, sex-, and age-based disparities.* Journal of the American Medical Association, 2004. **291**(22): p. 2720-2726.

66.     Whitney, S.N., *The shell game: How institutional review boards shuffle words.* Journal of Translational Medicine, 2014. **12**: p. 201.

67.     Walker, S. and S. Read, *Accessing vulnerable research populations: an experience with gatekeepers of ethical approval.* International Journal of Palliative Nursing, 2011. **17**(1): p. 14-18.

68.     Kirkwood, K., *On the exploitation of research subjects.* Journal of Clinical Research & Bioethics, 2013. **2012**.

69.     Kipnis, K., *Seven vulnerabilities in the pediatric research subject.* Theoretical Medicine and Bioethics, 2003. **24**(2): p. 107-120.

70.     Hurst, S., *Clarifying Vulnerability: The Case of Children.* Asian Bioethics Review, 2015. **7**(2): p. 126-138.

71.     Eriksson, S., A.T. Höglund, and G. Helgesson, *Do ethical guidelines give guidance? A critical examination of eight ethics regulations.* Cambridge Quarterly of Healthcare Ethics, 2008. **17**(1): p. 15-29.

72.     Hurst, S., *Clarifying Vulnerability: The Case of Children.* Asian Bioethics Review Asian Bioethics Review, 2015. **7**(2): p. 126-138.

73.     Luna, F. and S. Vanderpoel, *Not the usual suspects: Addressing layers of vulnerability.* Bioethics, 2013. **27**(6): p. 325-32.

74.     Hoffmaster, B., *What Does Vulnerability Mean?* Hastings Center Report, 2006. **36**(2): p. 38-45.

75.     Gouinlock, J., *The moral writings of John Dewey*. 1994, Amherst, NY: Prometheus Books.

76.     Bernstein, R.J., *Beyond objectivism and relativism: Science, hermeneutics, and praxis*. 2011: University of Pennsylvania Press.

77.     Schwandt, T.A., *The SAGE dictionary of qualitative inquiry*. 2007, Los Angeles, Calif.: Sage Publications.

78.     Savulescu, J., *Bioethics: Why philosophy is essential for progress.* Journal of Medical Ethics, 2015. **41**(1): p. 28-33.

79.     Moreno, J.D., *Bioethics is a naturalism*, in *Pragmatic Bioethics*, G. McGee, Editor. 1999, The MIT Press: United States of America. p. 3-16.

80.     Racine, E., *Which naturalism for bioethics? A defense of moderate (pragmatic) naturalism.* Bioethics, 2008. **22**(2): p. 92-100.

81.     Racine, E., *Pragmatic neuroethics: Improving treatment and understanding of the mind-brain*. 2010: MIT Press.

82.     Miller, F.G., J.J. Fins, and M.D. Bacchetta, *Clinical pragmatism: John Dewey and clinical ethics.* Journal of Contemporary Health Law and Policy, 1996. **13**(27): p. 27-51.

83.     Goldkuhl, G., *Meanings of Pragmatism: Ways to conduct information systems research.* Action in Language, Organisations and Information Systems, 2004.

84.     Wolf, S.M., *Shifting paradigms in bioethics and health law: the rise of a new pragmatism.* American Journal of Law & Medicine, 1994. **20**(4): p. 395-415.

85.     Misak, C., *The American Pragmatists*. 2013, New York, NY: Oxford University Press.

86.    Brendel, D.H. and F.G. Miller, *A plea for pragmatism in clinical research ethics.* American Journal of Bioethics, 2008. **8**(4): p. 24-31.

87.    Zizzo, N., E. Bell, and E. Racine, *What Is Everyday Ethics? A Review and a Proposal for an Integrative Concept.* The Journal of Clinical Ethics, 2016. **27**(2): p. 117.

88.    Hsieh, H.F. and S.E. Shannon, *Three approaches to qualitative content analysis.* Qualitative Health Research, 2005. **15**(9): p. 1277-88.

89.    Forman, J. and L. Damschroder, *Qualitative content analysis.* Empirical Research for Bioethics: A Primer. Oxford, UK: Elsevier Publishing, 2008: p. 39-62.

90.    Neuendorf, K.A., *The content analysis guidebook.* 2002, Thousand Oaks, CA: Sage.

91.    McDougall, R., *Reviewing Literature in Bioethics Research: Increasing Rigour in Non-Systematic Reviews.* Bioethics, 2015. **29**(7): p. 523-528.

92.    Coleman, C.H., *Vulnerability as a regulatory category in human subject research.* The Journal of Law, Medicine and Ethics, 2009. **37**(1): p. 12-18.

93.    Zimmerman, E. and E. Racine, *Ethical issues in the translation of social neuroscience: A policy analysis of current guidelines for public dialogue in human research.* Accountability in Research: Policies and Quality Assurance, 2012. **19**(1): p. 27-46.

94.    Office for Human Research Protections. *International Compilation of Human Research Standards.* 2016 February 16, 2016 [cited 2016 January 6, 2016]; Available from: http://www.hhs.gov/ohrp/international/index.html.

95.    Wrigley, A., *An eliminativist approach to vulnerability.* Bioethics, 2015. **29**(7): p. 478-487.

96.    Loue, S. and B. Loff, *Is there a universal understanding of vulnerability? Experiences with Russian and Romanian trainees in research ethics.* Journal of Empirical Research on Human Research Ethics, 2013. **8**(5): p. 17-27.

97.    Sengupta, S., et al., *How researchers define vulnerable populations in HIV/AIDS clinical trials.* AIDS and Behavior, 2010. **14**(6): p. 1313-1319.

98.    Deslauriers, C., et al., *Perspectives of Canadian researchers on ethics review of neuroimaging research.* Journal of Empirical Research on Human Research Ethics, 2010. **5**(1): p. 49-66.

99.    Luna, F., *Rubens, Corsets and Taxonomies: A Response to Meek Lange, Rogers and Dodds.* Bioethics, 2015. **29**(6): p. 448-450.

100.   DeBruin, D.A., J. Liaschenko, and A. Fisher, *How clinical trials really work rethinking research ethics.* Kennedy Institute of Ethics Journal, 2011. **21**(2): p. 121-39.

101.   Arras, J.D., *Rorty's pragmatism and bioethics.* The Journal of Medicine and Philosophy, 2003. **28**(5-6): p. 597-613.

102.   CIOMS, *International ethical guidelines for biomedical research involving human subjects.* 2002, CIOMS: Geneva, Switzerland.

103.   *Federal policy for the protection of human subjects; Proposed rules*, in *8 Federal Register 173*.

104.   Emanuel, E.J., D. Wendler, and C. Grady, *What makes clinical research ethical?* JAMA, 2000. **283**(20): p. 2701-11.

105.   Saul, J.R., *The Comeback: How Aboriginals Are Reclaiming Power And Influence*. 2014: Penguin Canada.

106.   Bewernick, B. and T. Schlaepfer, *Update on Neuromodulation for Treatment-Resistant Depression [version 1; referees: 3 approved]*. Vol. 4. 2015.

107. Dunn, L.B., et al., *Ethical Issues in Deep Brain Stimulation Research for Treatment-Resistant Depression: Focus on Risk and Consent.* American Journal of Bioethics Neuroscience, 2011. **2**(1): p. 29-36.

108. Alterman, R.L., D. Dumitriu, and S. Mathew, *Deep brain stimulation for major depressive disorder.* Clinical Neuropsychiatry, 2009. **6**: p. 259-65.

109. Bell, E., et al., *Ethical issues in psychiatric applications of deep brain stimulation: Learning from Canadian healthcare providers.* Journal of Ethics in Mental Health, 2011. **6**: p. 1-10.

110. Leykin, Y., et al., *Participants' Perceptions of Deep Brain Stimulation Research for Treatment-Resistant Depression: Risks, Benefits, and Therapeutic Misconception.* American Journal of Bioethics Primary Research, 2011. **2**(4): p. 33-41.

111. Kuhn, J., et al., *Deep brain stimulation as a new therapeutic approach in therapy-resistant mental disorders: ethical aspects of investigational treatment.* European Archives of Psychiatry and Clinical Neuroscience, 2009. **259 Suppl 2**: p. S135-41.

112. Manduca-Barone, A., *Including Appreciation and Voluntariness: The Other Two Elements of Decision-Making Capacity.* American Journal of Bioethics Neuroscience, 2011. **2**(1): p. 43-45.

113. Nuttin, B., et al., *Consensus on guidelines for stereotactic neurosurgery for psychiatric disorders.* Journal of Neurology, Neurosurgery & Psychiatry, 2014. **85**(9): p. 1003-1008.

114. Humphreys, K., J.C. Blodgett, and L.W. Roberts, *The exclusion of people with psychiatric disorders from medical research.* Journal of Psychiatric Research, 2015. **70**: p. 28-32.

115. Weijer, C., *Selecting subjects for participation in clinical research: One sphere of justice.* Journal of Medical Ethics 1999. **25**: p. 31-36.

116. Bell, E., G. Mathieu, and E. Racine, *Preparing the ethical future of deep brain stimulation.* Surgical Neurology, 2009. **72**(6): p. 577-586.

117. Fisher, C.E., et al., *The ethics of research on deep brain stimulation for depression: decisional capacity and therapeutic misconception.* Annals of the New York Academy of Sciences, 2012. **1265**: p. 69-79.

118. Kottow, M.H., *The vulnerable and the susceptible.* Bioethics, 2003. **17**(5-6): p. 460-471.

119. Kottow, M.H., *Vulnerability: what kind of principle is it?* Medicine, Health Care and Philosophy, 2004. **7**(3): p. 281-7.

120. McDonald, M. and S. Cox, *Moving toward evidence-based human participant protection.* Journal of Academic Ethics, 2009. **7**(1-2): p. 1-16.

121. McDonald, M., *Canadian governance of health research involving human subjects: is anybody minding the store?* Health Law Journal, 2001. **9**: p. 1-21.

122. Owen, M., C. Emerson, and P. Kolpack, *Informing governance through evidencebased research on REBs: challenges and opportunities.* Health Law Review, 2009. **17**: p. 40-46.

123. Hirtle, M., *The Governance of Research Involving Human Participants in Canada.* Health Law Journal, 2003. **11**: p. 137-52.

124. Kalichman, M., *Evidence-based research ethics.* American Journal of Bioethics, 2009. **9**(6-7): p. 85-87.

125. Anderson, E.E. and J.M. DuBois, *IRB decision-making with imperfect knowledge: a framework for evidence-based research ethics review.* The Journal of Law, Medicine & Ethics, 2012. **40**(4): p. 951-969.

126.   Wilson, R., et al., *Evidence-based research ethics and determinations of " engagement in research".* IRB, 2014. **36**(2): p. 10.

127.   Anderson, E.E. and J.M. DuBois, *The need for evidence-based research ethics: A review of the substance abuse literature.* Drug and Alcohol Dependence, 2007. **86**(2-3): p. 95-105.

128.   Roberts, L., *Evidence-based ethics and informed consent in mental illness research.* Archives of General Psychiatry, 2000. **57**(6): p. 540-542.

129.   Racine, E., et al., *A Canadian Perspective on Ethics Review and Neuroimaging: Tensions and Solutions.* Canadian Journal of Neurological Sciences, 2011. **38**(04): p. 572-579.

130.   Sackett, D.L., et al., *Evidence based medicine: What it is and what it isn't.* British Medical Journal, 1996. **312**(7023): p. 71-72.

131.   Emanuel, E.J., et al., *Oversight of human participants research: Identifying problems to evaluate reform proposals.* Annals of Internal Medicine, 2004. **141**(4): p. 282-91.

132.   Panel on Research Ethics. *Past Public Participation.* December 7, 2010 [cited 2016 August 5, 2016]; Available from: http://www.pre.ethics.gc.ca/eng/archives/participation/Default/.

133.   Subgroup on Procedural Issues for the TCPS (ProGroup): A Working Committee of the Interagency Advisory Panel on Research Ethics (PRE), *Proportionate approach to research ethics review in the TCPS: Proposed textual changes for the concept of vulnerability in the TCPS.* 2008: Ottawa, ON.

134.   Cox, S.M. and M. McDonald, *Ethics is for human subjects too: Participant perspectives on responsibility in health research.* Social Science & Medicine, 2013. **98**: p. 224-31.

135.   Gustafson, D.L. and F. Brunger, *Ethics, "vulnerability," and feminist participatory action research with a disability community.* Qualitative Health Research, 2014: p. 997-1005.

136.   Miller, F.G. and A. Wertheimer, *Facing up to paternalism in research ethics.* Hastings Center Report, 2007. **37**(3): p. 24-34.

137.   McDonald et al., M., *The governance of health research involving human subjects*. 2000: Ottawa.

138.   McGee, G., *Pragmatic Bioethics*. 2003: MIT press.

139.   Hester, D.M., *Is pragmatism well-suited to bioethics?* The Journal of Medicine and Philosophy, 2003. **28**(5-6): p. 545-561.

140.   Shook, J.R. and T. Solymosi, *Pragmatist neurophilosophy: American philosophy and the brain*. 2014: Bloomsbury.

# Appendices

Appendix 4-1: Descriptions of our primary codes for Manuscript 1, representing the four major content areas on vulnerability.

| Code | Description |
|---|---|
| Definitions | Captured explicit definitions of vulnerability and vulnerable subjects. It also captured instances of language implicitly qualifying a definition of vulnerability even where this may not have been explicitly provided. This 'qualifying' language was defined as that which suggests differing degrees or types of vulnerability. |
| Justifications | Captured explicit ethical reasons provided for the moral importance of vulnerability and responses to vulnerable groups. We also analyzed the moral status of vulnerability in the policies, as either (1) a fundamental ethical principle itself, (2) an application of another (or other) fundamental principle(s), or (3) a concern for ethics review with no explicit ethical status. |
| Groups and sources | Captured groups identified as vulnerable, as well as explanations for this identification, when provided. To further organize this data, we categorized groups into two types (social condition, e.g., subordinate members of hierarchies, and patient condition, e.g., children). We also captured sources of vulnerability identified independently from vulnerable groups. |
| Implications | Captured implications of vulnerability identified in the documents, including practical responses to vulnerable research participants and broader considerations for the ethical inclusion of vulnerable persons in research. To further structure these data we grouped implications by theme. |